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USMLE®

STEP 2 CK

Clinical Knowledge

Ninth Edition

A STUDENT-TO-STUDENT GUIDE

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- Rapid review section for last-minute cramming
- Includes hundreds of color clinical images and illustrations

Mc Graw Hill Education

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USMLE Step 2 CK

Ninth Edition

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SECTION 1

GUIDE TO EFFICIENT EXAM PREPARATION

Introduction 2

USMLE Step 2 CK—Computer-Based Testing Basics 2

How Will the cBT Be Structured? 2

Testing conditions: What Will the cBT Be Like? 3

What does the cBT Format Mean For Me? 3

How do I Register To Take the Examination? 4

What If I Need To Reschedule the Examination? 5

What About Time? 5

Security Measures 6

If I Leave during the Examination, What Happens To My Score? 6

What Types of Questions Are Asked? 6

How Long Will I Have To Wait Before I Get My Scores? 7

How Are the Scores Reported? 7

Defining Your Goal 7

When To Take the Exam 9

Study Resources 11

Quality considerations 11

clinical Review Books 11

Test Banks 11

Texts and Notes 12

commercial courses 12

NBME/USMLE Publications 12

Test-Day Checklist 12

Things To Bring With You To the Exam 12

Testing Agencies 13

Introduction

The United States Medical Licensing Examination (USMLE) Step 2 allows you to pull together your clinical experience on the wards with the numerous "factoids" and classical disease presentations that you have memorized over the years. Whereas Step 1 stresses basic disease mechanisms and principles, Step 2 places more emphasis on clinical diagnosis and management, disease pathogenesis, and preventive medicine. The Step 2 examination is now composed of 2 parts:

- The Step 2 Clinical Knowledge examination (Step 2 CK)
- The Step 2 Clinical Skills examination (Step 2 CS)

The USMLE Step 2 CK is the second of three examinations that you must pass in order to become a licensed physician in the United States. The computerized Step 2 CK is a 1-day (9-hour) multiple-choice examination.

KEY FACT

The goal of the Step 2 CK is to apply your knowledge of medical facts to clinical scenarios you may encounter as a resident.

Students are also required to take the Step 2 CS, a 1-day live examination in which students examine 12 standardized patients. For more information on this examination, please refer to First Aid for the USMLE Step 2 CS. Information about the Step 2 CS format and about eligibility, registration, and scoring can be found at http://www.nbme.org.

The information found in this section as well as in the remainder of the book will address only the Step 2 CK.

USMLE Step 2 CK—Computer-Based Testing Basics

HOW WILL THE CBT BE STRUCTURED?

The Step 2 CK is a computer-based test (CBT) administered by Prometric, Inc. It is a 1-day examination with approximately 352 questions divided into eight 60-minute blocks of 44 questions each, administered in a single 9-hour testing session. Some sections may have more or fewer than 44 questions, but the maximum question total for the exam is 355. The Step 2 CK uses the same **FRED v2** software program as that used on the USMLE Step 1 examination.

Three question styles predominate throughout the examination. The most common format is **Single One Best Answer** questions. This is the traditional multiple-choice format in which you are tasked with selecting the "most correct" answer. Another common style is **Matching Sets.** These questions consist of a series of questions related to a similar topic or prompt. Finally, **"Sequential Item Sets"** have been introduced to the examination. These are sets of multiple-choice questions that are related and must all be answered in sequence without skipping a question in the set along the way. As you answer questions in a given set, the previous answers become locked and cannot be changed. These are the only questions on the USMLE examination that are locked in such a way. There will be no more than 5 Sequential Item Sets within each USMLE Step 2 CK examination. In 2011, the USMLE examination introduced Sequential Item Sets that include a pharmaceutical ad or an abstract on which the questions are based.

During the time allotted for each block on the USMLE Step 2 CK, the examinee can answer test questions in any order and can also review responses and change answers (with the exception of responses within the Sequential Item

Sets described above). However, under no circumstances can examinees return to previous blocks and change answers. Once an examinee has finished a block, he or she must click on a screen icon in order to continue to the next block. Time not used during a testing block will be added to the examinee's overall break time, but it cannot be used to complete other testing blocks.

KEY FACT

Expect to spend up to 9 hours at the test center.

TESTING CONDITIONS: WHAT WILL THE CBT BE LIKE?

Even if you're familiar with computer-based testing and the Prometric test centers, FRED v2 is a testing format that you should access from the USMLE Web site (http://www.usmle.org) and try out prior to the examination. If you familiarize yourself with the FRED v2 testing interface ahead of time, you can skip the 15-minute tutorial offered on examination day and add those minutes to your allotted break time of 45 minutes.

For security reasons, examinees are not allowed to bring personal equipment (except those needed for medical reasons and soft-foam earplugs as detailed below) into the testing area—which means that writing implements, outerwear, watches (even analog), cellular telephones, and electronic paging devices are all prohibited. Food and beverages are prohibited as well. The proctor will assign you a small locker in which you can store your belongings and any food you bring for the day. Examinees will also be given 2 (8″ × 11″) laminated writing surfaces, pens, and erasers for note taking and for recording their test Candidate Identification Number (CIN). These materials must be returned after the examination. Testing centers are monitored by audio and video surveillance equipment. Each time you enter the testing room, you will have to undergo a screening process to ensure that you are not bringing in personal items.

You should become familiar with a typical question screen. A window to the left displays all the questions in the block and shows you the unanswered questions (marked with an "i"). Some questions will contain figures, color illustrations, audio, or video adjacent to the question. Although the contrast and brightness of the screen can be adjusted, there are no other ways to manipulate the picture (eg, zooming or panning). Larger images are accessed with an **"exhibit"** button. The examinee can also call up a window displaying normal **lab values.** You may **mark** questions to review at a later time by clicking the check mark at the top of the screen. The **annotation** feature functions like the provided dry erase sheets and allows you to jot down notes during the examination. Play with the **highlighting/strike-out** and annotation features with the vignettes and multiple answers.

You should also do a few practice blocks to determine which tools actually help you process questions more efficiently and accurately. If you find that you are not using the marking, annotation, or highlighting tools, then **keyboard shortcuts** can be quicker than using a mouse. Headphones are provided for listening to audio and blocking outside noise. Alternatively, examinees can bring soft earplugs to block excess noise. These earplugs must be examined by Prometric staff before you are allowed to take them into the testing area.

KEY FACT

Keyboard shortcuts:

- A–E—Letter choices.
- Enter or space bar—Move to the next question.
- Esc—Exit pop-up Lab and Exhibit windows.
- Alt-T—Countdown and time-elapsed clocks for current session and overall test.

WHAT DOES THE CBT FORMAT MEAN FOR ME?

The CBT format is the same format as that used on the USMLE Step 1. If you are uncomfortable with this testing format, spend some time playing with a Windows-based system and pointing and clicking icons or buttons with a mouse.

The USMLE also offers students an opportunity to take a simulated test, or practice session, at a Prometric center. The session is divided into three 1-hour blocks of 50 test items each. The 143 Step 2 CK sample test items that are available on the USMLE Web site (http://www.usmle.org) are the same as those used at CBT practice sessions. **No new items are presented.** The cost is about $52 for US and Canadian students but is higher for international students. Students receive a printed percent-correct score after completing the session. No explanations of questions are provided. You may register for a practice session online at http://www.usmle.org.

The National Board of Medical Examiners (NBME) provides another option for students to assess their Step 2 CK knowledge with the Comprehensive Clinical Science Self-Assessment (CCSSA) test. This test is available on the NBME Web site in several versions for $50, or $60 for expanded feedback, which will display at the end of the exam all of the questions you answered incorrectly, without additional explanations. The content of the CCSSA items resembles that of the USMLE Step 2 CK. Upon completion of the CCSSA, users will be provided with a performance profile indicating their strengths and weaknesses. This feedback is intended for use as a study tool only and is not necessarily an indicator of Step 2 CK performance. For more information on the CCSSA examination, visit the NBME's Web site at http://www.nbme.org, and click on the link for "NBME Web-based Self-Assessment Service."

HOW DO I REGISTER TO TAKE THE EXAMINATION?

Information on Step 2 CK format, content, and registration requirements can be found on the USMLE Web site. To register for the examination, students/graduates of accredited schools in the United States and Canada can apply online at the NBME Web site (http://www.nbme.org), whereas students/graduates of non-US/Canadian schools should apply through the Educational Commission for Foreign Medical Graduates ECFMG (https://iwa2.ecfmg.org). A printable version of the application is also available on these sites. The preliminary registration process for the USMLE Step 2 CK is as follows:

- Complete a registration form, and send your examination fees to the NBME (online).
- Select a 3-month block in which you wish to be tested (eg, June/July/August).
- Attach a passport-type photo to your completed application form.
- Complete a Certification of Identification and Authorization form. This form must be signed by an official at your medical school such as the registrar's office (if you are a student) or a notary public (if you have graduated) to verify your identity. It is valid for 5 years, allowing you to use only your USMLE identification number for future transactions.
- Send your certified application form to the NMBE for processing. (Applications may be submitted more than 6 months before the test date, but examinees will not receive their scheduling permits until 6 months prior to the eligibility period.)
- The NBME will process your application within 4–6 weeks and will send you a slip of paper that will serve as your scheduling permit.
- Once you have received your scheduling permit, decide when and where you would like to take the examination. For a list of Prometric locations nearest you, visit https://www.prometric.com.
- Call Prometric's toll-free number or visit https://www.prometric.com to arrange a time to take the examination.
- The Step 2 CK is offered on a year-round basis except for the first 2 weeks

in January. For the most up-to-date information on available testing days at your preferred testing location, refer to http://www.usmle.org.

The scheduling permit you receive from the NBME will contain the following important information:

- Your USMLE identification number.
- The eligibility period during which you may take the examination.
- Your "scheduling number," which you will need to make your examination appointment with Prometric.
- Your CIN, which you must enter at your Prometric workstation in order to access the examination.

Prometric has no access to the codes and will not be able to supply these numbers, so **do not lose your permit!** You will not be allowed to take the Step 2 CK unless you present your permit along with an unexpired, government-issued photo identification that contains your signature (eg, driver's license, passport). Make sure the name on your photo ID exactly matches the name that appears on your scheduling permit.

KEY FACT

Because the Step 2 CK examination is scheduled on a "first-come, first-served" basis, you should be sure to call Prometric as soon as you receive your scheduling permit.

WHAT IF I NEED TO RESCHEDULE THE EXAMINATION?

You can change your date and/or center within your 3-month period by contacting Prometric if space is available. If you reschedule 31 days before your scheduled testing date, there is no fee; between 6 and 30 days before, there is a $50 fee; 5 or fewer days before, there is a larger fee. If you need to reschedule outside your initial 3-month period, you can apply for a single 3-month extension (eg, April/May/June can be extended through July/August/September) after your eligibility period has begun (visit http://www.nbme.org for more information). This extension currently costs $70. For other rescheduling needs, you must submit a new application along with another application fee.

WHAT ABOUT TIME?

Time is of special interest on the CBT examination. Here is a breakdown of the examination schedule:

Tutorial	15 minutes
60-minute question blocks (44 questions per block)	8 hours
Break time (includes time for lunch)	45 minutes
Total test time	9 hours

The computer will keep track of how much time has elapsed during the examination. However, the computer will show you only how much time you have remaining in a given block. Therefore, it is up to you to determine if you are pacing yourself properly.

The computer will not warn you if you are spending more than the 45 minutes allotted for break time. The break time includes not only the usual concept of a break—when you leave the testing area—but also the time it takes for you to make the transition to the next block, such as entering your CIN or even taking a quick stretch. **If you do exceed the 45-minute break time, the time to complete the last block of the test will be reduced.** However, you can elect not to use all of your break time, or you can gain extra break time either by skipping the tutorial or by finishing a block ahead of the allotted time.

SECURITY MEASURES

Smile! The NBME uses a check-in/check-out process that includes electronic capture of your fingerprints and photograph. These measures are intended to increase security by preventing fraud, thereby safeguarding the integrity of the examination. The new procedures also decrease the amount of time needed to check in and out of the examination throughout the day, thereby maximizing your break time. However, you still need to sign out and sign in with the Test Center Log when exiting and entering the testing area.

IF I LEAVE DURING THE EXAMINATION, WHAT HAPPENS TO MY SCORE?

You are considered to have started the examination once you have entered your CIN onto the computer screen. In order to receive an official score, however, you must finish the entire examination. This means that you must start and either finish or run out of time for each block of the examination. If you do not complete all the question blocks, your examination will be documented on your USMLE score transcript as an incomplete attempt, but no actual score will be reported.

The examination ends when all blocks have been completed or time has expired. As you leave the testing center, you will receive a written test completion notice to document your completion of the examination.

WHAT TYPES OF QUESTIONS ARE ASKED?

The Step 2 CK is an integrated examination that tests understanding of normal conditions, disease categories, and physician tasks. Almost all questions on the examination are case based. A substantial amount of extraneous information may be given, or a clinical scenario may be followed by a question that could be answered without actually requiring that you read the case. It is your job to determine which information is superfluous and which is pertinent to the case at hand. Content areas include internal medicine, OB/GYN, pediatrics, preventive services, psychiatry, surgery, and other areas relevant to the provision of care under supervision. Physician tasks are distributed as follows:

- Establishing a diagnosis (25–40%)
- Understanding the mechanisms of disease (20–35%)
- Applying principles of management (15–25%)
- Promoting preventive medicine and health maintenance (15–25%)

Most questions on the examination have a **Single Best Answer** format, but some **Matching Sets** and **Sequential Item Sets** will be found throughout the examination. Regardless of the question format, the part of the vignette that actually asks the question—the **stem**—is usually found at the end of the scenario and generally relates to the physician task. From student experience, there are a few stems that are consistently addressed throughout the examination:

- What is the most likely diagnosis? (40%)
- Which of the following is the most appropriate initial step in management? (20%)
- Which of the following is the most appropriate next step in management? (20%)
- Which of the following is the most likely cause of … ? (5%)
- Which of the following is the most likely pathogen … ? (3%)
- Which of the following would most likely prevent … ? (2%)
- Other (10%)

Additional examination tips are as follows:

- Note the age and race of the patient in each clinical scenario. When ethnicity is given, it is often relevant. Know these well (see high-yield facts), especially for more common diagnoses.
- Be able to recognize key facts that distinguish major diagnoses.
- Questions often describe clinical findings rather than naming eponyms (eg, they cite "audible hip click" instead of "positive Ortolani sign").
- Questions about acute patient management (eg, trauma) in an emergency setting are common.

The cruel reality of the Step 2 CK is that no matter how much you study, there will still be questions you will not be able to answer with confidence. If you recognize that a question cannot be solved in a reasonable period of time, make an educated guess and move on; you will not be penalized for guessing. Also bear in mind that some of the USMLE examination questions are "experimental" and will not count toward your score.

HOW LONG WILL I HAVE TO WAIT BEFORE I GET MY SCORES?

The USMLE reports scores 3–4 weeks after the examinee's test date. During peak periods, however, as many as 6 weeks may pass before reports are scored. Official information concerning the time required for score reporting is posted on the USMLE Web site, http://www.usmle.org.

HOW ARE THE SCORES REPORTED?

Like the Step 1 score report, your Step 2 CK report includes your pass/fail status, a numeric score, and a performance profile organized by discipline and disease process (see Figures 1-1A and 1-1B). The score is a 3-digit scaled score based on a predefined proficiency standard. As of July 1, 2014, the required passing score is 209. This score requires answering 60–70% of questions correctly. Any adjustments in the required passing score will be available on the USMLE Web site.

Defining Your Goa

The first and most important thing to do in your Step 2 CK preparation is define how well you want to do on the exam, as this will ultimately determine the extent of preparation that will be necessary. The amount of time spent in preparation for this examination varies widely among medical students. Possible goals include the following:

- **Simply passing.** This goal meets the requirements for becoming a licensed physician in the United States. However, if you are taking the Step 2 CK in a time frame in which residency programs will see your score, you should strive to do as well as or better than you did on Step 1.
- **Beating the mean.** This signifies an ability to integrate your clinical and factual knowledge to an extent that is superior to that of your peers (around 240 for recent examination administrations). Others redefine this goal as achieving a score 1 standard deviation above the mean (usually in the range of 245–250). Highly competitive residency programs may use your Step 1 and Step 2 scores (if available) as a screening tool or as a selection requirement (see Figure 1-2). International medical graduates should aim to beat the mean, as USMLE scores are likely to be a selection factor even for less competitive US residency programs.

USMLE United States Medical Licensing Examination

UNITED STATES MEDICAL LICENSING EXAMINATION ®

STEP 2 CLINICAL KNOWLEDGE (CK) SCORE REPORT

This score report is provided for the use of the examinee.
Third party users of USMLE information are advised to rely solely on official USMLE transcripts.

Schmoe, Joe

USMLE ID: 1-234-567-8 Test Date: July 2014

The USMLE is a single examination program consisting of three Steps designed to assess an examinee's understanding of and ability to apply concepts and principles that are important in health and disease and that constitute the basis of safe and effective patient care. Step 2 is designed to assess whether an examinee can apply medical knowledge, skills, and understanding of clinical science essential for the provision of patient care under supervision, including emphasis on health promotion and disease prevention. The inclusion of Step 2 in the USMLE sequence is intended to ensure that due attention is devoted to principles of clinical sciences and basic patient-centered skills that provide the foundation for the safe and competent practice of medicine. There are two components to Step 2: a Clinical Knowledge (CK) examination and a Clinical Skills (CS) examination. This report represents results for the Step 2 CK examination only. Results of the examination are reported to medical licensing authorities in the United States and its territories for use in granting an initial license to practice medicine. This score§ represents your result for the administration of Step 2 CK on the test date shown above.

PASS	This result is based on the minimum passing score recommended by USMLE for Step 2 CK. Individual licensing authorities may accept the USMLE-recommended pass/fail result or may establish a different passing score for their own jurisdictions.

270	This score is determined by your overall performance on Step 2 CK. For recent administrations, the mean and standard deviation for first-time examinees from U.S. and Canadian medical schools are approximately 238 and 19, respectively, with most scores falling between 140 and 260. A score of 209 is set by USMLE to pass Step 2 CK. The standard error of measurement (SEM)‡ for this scale is six points.

§Effective April 1, 2013, test results are reported on a three-digit scale only. Test results reported as passing represent an exam score of 75 or higher on a two-digit scoring scale.

‡Your score is influenced both by your general understanding of clinical science and the specific set of items selected for this Step 2 CK examination. The Standard Error of Measurement (SEM) provides an index of the variation in scores that would be expected to occur if an examinee were tested repeatedly using different sets of items covering similar content.

FIGURE 1-1A. Sample score report—front page.

- **Acing the exam.** Perhaps you are one of those individuals for whom nothing less than the best will do—and for whom excelling on standardized examinations is a source of pride and satisfaction. A high score on the Step 2 CK might also represent a way to strengthen your application and "make up" for a less-than-satisfactory score on Step 1.
- **Evaluating your clinical knowledge.** In many ways, this goal should serve as the ultimate rationale for taking the Step 2 CK, as it is technically the reason the examination was initially designed. The case-based nature of the Step 2 CK differs significantly from the more fact-based Step 1 examination in that it more thoroughly assesses your ability to recognize classic clinical presentations, deal with emergent situations, and follow the step-by-step thought processes involved in the treatment of particular diseases.
- **Preparing for internship.** Studying for the USMLE Step 2 CK is an excellent way to review and consolidate all of the information you have learned in preparation for internship.

INFORMATION PROVIDED FOR EXAMINEE USE ONLY

The Performance Profile below is provided solely for the benefit of the examinee.
These profiles are developed as self-assessment tools for examinees only and will not be reported or verified to any third party.

USMLE STEP 2 CK PERFORMANCE PROFILE

	Lower Performance	Borderline Performance	Higher Performance
PHYSICIAN TASK PROFILE			
Preventive Medicine & Health Maintenance			xxxxxxxxxxxxxxxxx
Understanding Mechanisms of Disease			xxxxxxxxxxxxx
Diagnosis			xxxxxxxxxxx
Principles of Management			xxxxxxxxxxxxx
NORMAL CONDITIONS & DISEASE CATEGORY PROFILE			
Normal Growth & Development; Principles of Care			xxxxxxxxxxxxxxxxx
Immunologic Disorders			xxxxxxxxxxxxxxxxxx
Diseases of Blood & Blood Forming Organs			xxxxxxxxxxxxxxxxxx
Mental Disorders			xxxxxxxxxxxxxxxx
Diseases of the Nervous System & Special Senses			xxxxxxxxxxxxxxx
Cardiovascular Disorders			xxxxxxxxxxxxxxx
Diseases of the Respiratory System			xxxxxxxxxxxxxxxxx
Nutritional & Digestive Disorders			xxxxxxxxxxxxxxxx
Gynecologic Disorders			xxxxxxxxxxxxxxxx
Renal, Urinary & Male Reproductive Systems			xxxxxxxxxxxxxxxx
Disorders of Pregnancy, Childbirth & Puerperium			xxxxxxxxxxxxxxxxxx
Musculoskeletal, Skin & Connective Tissue Diseases			xxxxxxxxxxxxxxxxx
Endocrine & Metabolic Disorders			xxxxxxxxxxxxxxxxx
DISCIPLINE PROFILE			
Medicine			xxxxxxxxx
Obstetrics & Gynecology			xxxxxxxxxxxxxxx
Pediatrics			xxxxxxxxxxxxx
Psychiatry			xxxxxxxxxxxxxxxx
Surgery			xxxxxxxxxxxxx

The above Performance Profile is provided to aid in self-assessment. The shaded area defines a borderline level of performance for each content area; borderline performance is comparable to a HIGH FAIL/LOW PASS on the total test.

Performance bands indicate areas of relative strength and weakness. Some bands are wider than others. The width of a performance band reflects the precision of measurement: narrower bands indicate greater precision. The band width for a given content area is the same for all examinees. An asterisk indicates that your performance band extends beyond the displayed portion of the scale. Small differences in the location of bands should not be over interpreted. If two bands overlap, performance in the associated areas should be interpreted as similar. Because Step 2 CK is designed to be integrative, many items contribute to more than one content area. As a consequence, caution should be used when interpreting differences in performance across content areas.

This profile should not be compared to those from other Step 2 CK administrations.

Additional information concerning the topics covered in each content area can be found in the USMLE Step 2 CK Content Description and Sample Test Materials.

FIGURE 1-1B. Sample score report—back page.

Matching statistics, including examination scores related to various specialties, are available at the National Resident Matching Program Web site at https://www.nrmp.org under “Match Data.”

WHEN TO TAKE THE EXAM

The second most important thing to do in your examination preparation is to decide when to take the examination. With the CBT, you now have a wide variety of options regarding when to take the Step 2 CK. Here are a few factors to consider:

- **The nature of your objectives,** as defined above.
- **The specialty to which you are applying.** It is clear that an increasing number of residency programs are viewing the Step 2 CK as an integral part of the residency application process. Several research publications

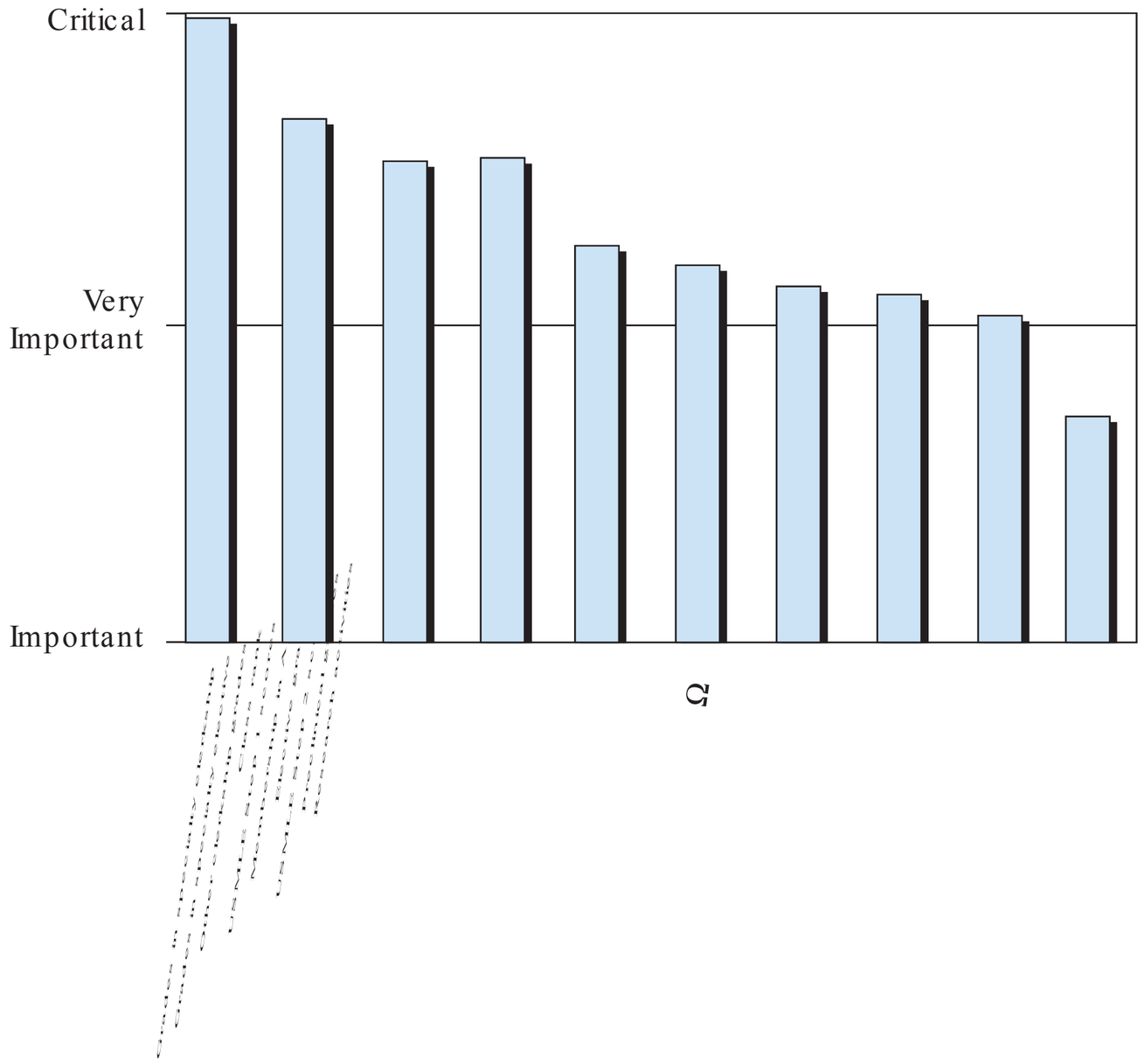


FIGURE 1-2. Academic factors important to residency directors.

demonstrate the increasing importance placed on this examination by residency directors. Some programs are now requiring the Step 2 CK score in order to rank candidates for a residency position. It is therefore in the best interest of candidates to have this examination done in time for scores to be available for the residency application. Taking the examination in June or July ensures that scores will be available for the Match period that begins in September. Some programs, however, will accept scores after the application process starts. Check with programs in your desired specialty to determine when to take the examination.

- **Prerequisite to graduation.** If passing the USMLE Step 2 CK is a prerequisite to graduation at your medical school, you will need to take the examination in the fall or winter at the latest.
- **Proximity to clerkships.** Many students feel that the core clerkship material is fresher in their minds early in the fourth year, making a good argument for taking the Step 2 CK earlier in the fall.
- **The nature of your schedule.**
- **Considerations for MD/PhD students.** The dates of passing the Step 1, Step 2, and Step 3 examinations should occur within a 7-year period. However, the typical pathway for MD/PhD students consists of 2–3 years of preclinical (and sometimes clinical) work in medical school, 3–4 years of graduate work with research, and finally returning to medical school for clinical work. MD/PhD students typically exceed the 7-year limit. Depending on the state in which licensure is sought, such students may need to petition their licensure body for an exception to this rule.

KEY FACT

The Step 2 CK is an opportunity to consolidate your clinical knowledge and prepare for internship.

Study Resources

QUALITY CONSIDERATIONS

Although an ever-increasing number of USMLE Step 2 CK review books and software packages are available on the market, the quality of this material is highly variable (see Section 3). Some common problems include the following:

- Some review books are too detailed to be reviewed in a reasonable amount of time or cover subtopics that are not emphasized on the examination (eg, a 400-page anesthesiology book).
- Many sample question books have not been updated to reflect current trends on the Step 2 CK.
- Many sample question books use poorly written questions, contain factual errors in their explanations, give overly detailed explanations, or offer no explanations at all.
- Software for boards review is of highly variable quality, may be difficult to install, and may be fraught with bugs.

CLINICAL REVIEW BOOKS

Many review books are available, so you must decide which ones to buy by carefully evaluating their relative merits. Toward this goal, you should compare differing opinions from other medical students; read the reviews and ratings in Section 3 of this guide; and examine the various books closely in the bookstore. Do not worry about finding the "perfect" book, as many subjects simply do not have one.

There are 2 types of review books: those that are stand-alone titles and those that are part of a series. Books in a series generally have the same style, and you must decide if that style is helpful for you and optimal for a given subject.

KEY FACT

The best review book for you reflects the way you like to learn. If a given review book is not working for you, stop using it no matter how highly rated it may be.

TEST BANKS

A test bank can serve multiple functions for examinees, including the following:

- Provide information about strengths and weaknesses in your fund of knowledge.
- Add variety to your study schedule.
- Serve as the main form of study.
- Improve test-taking skills.
- Familiarize examinees with the style of the USMLE Step 2 CK examination.

Students report that some test banks have questions that are, on average, shorter and less clinically oriented than those on the current Step 2 CK. Step 2 CK questions demand fast reading skills and the application of clinical facts in a problem-solving format. Approach sample examinations critically, and do not waste time with low-quality questions until you have exhausted better sources.

KEY FACT

Use test banks to identify concepts and areas of weakness, not just facts that you missed.

After you have taken a practice test, try to identify concepts and areas of weakness, not just the facts that you missed. Use this experience to motivate your study and to prioritize the areas in which you need the most work. Analyze

the pattern of your responses to questions to determine if you have made systematic errors in answering questions. Common mistakes include reading too much into the question, second-guessing your initial impression, and misinterpreting the question.

TEXTS AND NOTES

Most textbooks are too detailed for high-yield boards review and should be avoided. When using texts or notes, engage in active learning by making tables, diagrams, new mnemonics, and conceptual associations whenever possible. If you already have your own mnemonics, do not bother trying to memorize someone else's. Textbooks are useful, however, to supplement incomplete or unclear material.

COMMERCIAL COURSES

Commercial preparation courses can be helpful for some students, as they offer an effective way to organize study material. However, multiweek courses are costly and require significant time commitment, leaving limited time for independent study. Also note that some commercial courses are designed for first-time test takers, students who are repeating the examination, or international medical graduates.

NBME/USMLE PUBLICATIONS

We strongly encourage students to use the free materials provided by the testing agencies and to study the following NBME publications:

- USMLE Step 2 Clinical Knowledge (CK): Content Description and General Information. This publication provides you with nuts-and-bolts details about the examination (included on the Web site http://www.usmle.org; free to all examinees).
- USMLE Step 2 Clinical Knowledge (CK): Sample Test Questions. This is a PDF version of the test questions and test content also found at http://www.usmle.org.
- **NBME Test Delivery Software (FRED) and Tutorial.** This includes 131 valuable practice questions. The questions are available as a download from the USMLE Web site. Make sure you are using the new version of FRED and not the older Prometric version.
- **USMLE Web site (http://www.usmle.org).** In addition to allowing you to become familiar with the CBT format, the sample items on the USMLE Web site provide the only questions that are available directly from the test makers. Student feedback varies as to the similarity of these questions to those on the actual exam, but they are nonetheless worthwhile to know.

Test-Day Checklist

THINGS TO BRING WITH YOU TO THE EXAM

- Be sure to bring your scheduling permit and a photo ID with signature. (You will not be admitted to the examination if you fail to bring your permit, and Prometric will charge a rescheduling fee.)
- Remember to bring lunch, snacks (for a little "sugar rush" on breaks), and fluids (including a caffeine-containing drink if needed).

- Bring clothes to layer to accommodate temperature variations at the testing center.
- Earplugs will be provided at the Prometric center.

Testing Agencies

National Board of Medical Examiners (NBME)
Department of Licensing Examination Services
3750 Market Street
Philadelphia, PA 19104-3102
(215) 590-9700
Fax: (215) 590-9460
http://www.nbme.org/contact/
e-mail: webmail@nbme.org

USMLE Secretariat
3750 Market Street
Philadelphia, PA 19104-3190
(215) 590-9700
Fax: (215) 590-9460
http://www.usmle.org
e-mail: webmail@nbme.org

Educational Commission for Foreign Medical Graduates (ECFMG)
3624 Market Street
Philadelphia, PA 19104-2685
(215) 386-5900
Fax: (215) 386-9196
http://www.ecfmg.org/contact.html
e-mail: info@ecfmg.org

Federation of State Medical Boards (FSMB)
400 Fuller Wiser Road, Suite 300
Euless, TX 76039
(817) 868-4041
Fax: (817) 868-4098
http://www.fsmb.org/contact-us
e-mail: usmle@fsmb.org

NOTES

SECTION 2

DATABASE OF HIGH-YIELD FACTS

Cardiovascular

Dermatology

Endocrinology

Epidemiology

Ethics and Legal Issues

Gastrointestinal

Hematology/Oncology

Infectious Disease

Musculoskeletal

Neurology

Obstetrics

Gynecology

Pediatrics

Psychiatry

Pulmonary

Renal/Genitourinary

Selected Topics in Emergency Medicine

Rapid Review

How to Use the Database

The ninth edition of First Aid for the USMLE Step 2 CK contains a revised and expanded database of clinical material that student authors and faculty have identified as high yield for boards review. The facts are organized according to subject matter, whether medical specialty (eg, Cardiovascular, Renal) or high-yield topic (eg, Ethics). Each subject is then divided into smaller subsections of related facts.

Individual facts are generally presented in a logical fashion, from basic definitions and epidemiology to **History/Physical Exam, Diagnosis,** and **Treatment.** Lists, mnemonics, pull quotes, vignette flash cards, and tables are used when they can help the reader form key associations. In addition, color and black-and-white images are interspersed throughout the text. At the end of Section 2, we also feature a Rapid Review chapter consisting of key facts and classic associations that can be studied a day or two before the exam.

The content contained herein is useful primarily for the purpose of reviewing material already learned. The information presented is not ideal for learning complex or highly conceptual material for the first time.

The Database of High-Yield Facts is not comprehensive. Use it to complement your core study material, not as your primary study source. The facts and notes have been condensed and edited to emphasize essential material. Work with the material, add your own notes and mnemonics, and recognize that not all memory techniques work for all students.

We update Section 2 biannually to keep current with new trends in boards content as well as to expand our database of high-yield information. However, we must note that inevitably many other high-yield entries and topics are not yet included in our database.

We actively encourage medical students and faculty to submit entries and mnemonics so that we may enhance the database for future students. We also solicit recommendations of additional study tools that may be useful in preparing for the examination, such as diagrams, charts, and computer-based tutorials (see How to Contribute, p. xiii).

DISCLAIMER

The entries in this section reflect student opinions of what is high yield. Owing to the diverse sources of material, no attempt has been made to trace or reference the origins of entries individually. We have regarded mnemonics as essentially in the public domain. All errors and omissions will gladly be corrected if brought to the attention of the authors, either through the publisher or directly by e-mail.

HIGH-YIELD FACTS IN

CARDIOVASCULAR

Electrocardiogram 18

Cardiac Physical Exam 20

Arrhythmias 21

- Bradyarrhythmias and Conduction Abnormalities 21
- Tachyarrhythmias 21

Congestive Heart Failure 22

- Systolic dysfunction 24
- Nonsystolic dysfunction 27

Cardiomyopathy 28

- dilated cardiomyopathy 28
- Hypertrophic cardiomyopathy 30
- Restrictive cardiomyopathy 30

Coronary Artery Disease 31

- Angina Pectoris 31

Acute Coronary Syndromes 32

- Unstable Angina/Non-ST-Elevation Myocardial Infarction 32
- ST-Elevation Myocardial Infarction 33

Dyslipidemia 35

Hypertension 37

- 1° (Essential) Hypertension 37
- 2° Hypertension 38
- Hypertensive crises 38

Pericardial Disease 39

- Pericarditis 39
- cardiac Tamponade 41

Valvular Heart Disease 42

Vascular Disease 42

- Aortic Aneurysm 42
- Aortic dissection 44
- deep Venous Thrombosis 45
- Peripheral Arterial disease 46
- Lymphedema 47

Syncope 47

Electrocardiogram

KEY FACT

Heart rate = 300 / number of large boxes between two consecutive QRS complexes.

Assess the ECG for rate, rhythm, axis, intervals, ischemia, and chamber enlargement (see Figure 2.1-1).

Rate

Normal adult HR is 60–100 bpm. HR < 60 bpm is **bradycardia.** HR > 100 bpm is **tachycardia.**

Rhythm

Sinus rhythm: Normal rhythm that originates from sinus node (ECG: P before every QRS and QRS after every P).

Axis

Can be determined by examining the QRS in leads I and aVF. Axis deviation can be a sign of ventricular hypertrophy or bundle branch block. See Table 2.1-1.

Intervals

- **PR interval:** Normally between 120 and 200 msec; in AV block PR interval > 200 msec (AV block can also present as P with no QRS afterward).
- **QRS interval:** Normally < 120 msec. Two important patterns that have a widened QRS are left and right bundle branch block:
  - **Left bundle branch block (LBBB):** QRS duration > 120 msec; deep S wave and no R wave in V_1; wide, tall R waves in I, V_5, and V_6 (see Figure 2.1-2).
  - **Right bundle branch block (RBBB):** QRS duration > 120 msec; RSR′ complex ("rabbit ears"); qR or R morphology with a wide R wave in V_1; QRS pattern with a wide S wave in I, V_5, and V_6 (see Figure 2.1-3).

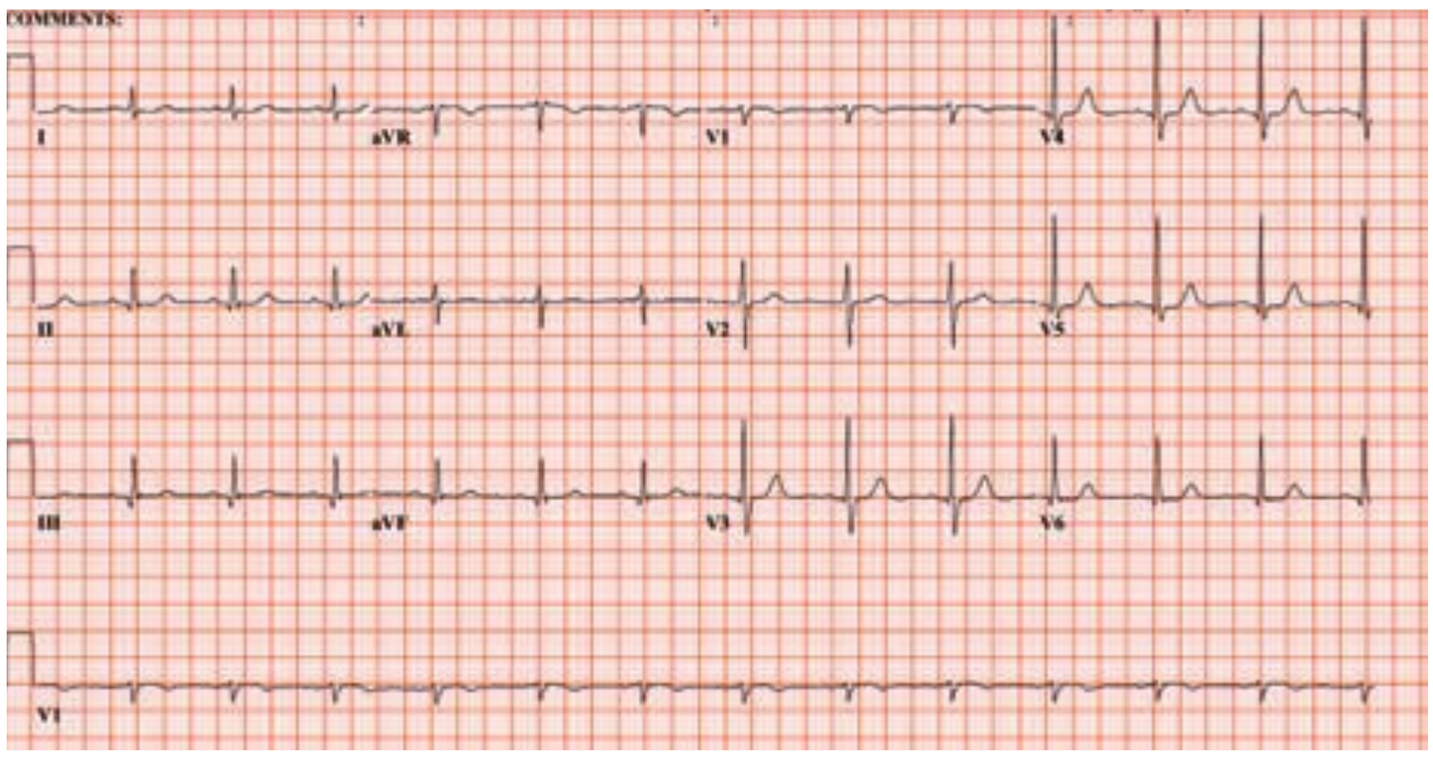


FIGURE 2.1-1. Normal electrocardiogram from a healthy subject. (Reproduced with permission from USMLE-Rx.com.)

TABLE 2.1-1. Axis Deviation by ECG Findings

	Lead I	Lead aVF	Degrees
Normal axis	↑	↑	⊖30–⊕90
Left axis deviation	↑	↓	≤ ⊖30
Right axis deviation	↓	↑	> ⊕90

- **QT interval:** Normally QTc (the QT interval corrected for extremes in heart rate) is < 440 msec. In long QT syndrome, QTc > 440 msec. Long QT syndrome is an underdiagnosed congenital disorder that is one cause of a long QT and predisposes to ventricular tachyarrhythmias.

Ischemia/Infarction

- **Acute ischemia:** Natural progression starts with T-wave inversion, progresses to ST-segment changes (either depression or elevation), and finally results in Q waves (> 40 msec or more than one-third of the QRS amplitude) on the ECG. Because of this, Q waves signify either acute or prior ischemic events and do not provide information on when an event took place.
- Poor R-wave progression in precordial waves can also be a sign of ischemia, although it is not specific. In a normal ECG, R waves increase in size compared to the S wave between leads V_1 and V_5. Poor R-wave progression refers to diminished R waves in these precordial leads.

Chamber Enlargement

- **Atrial enlargement:**
  - **Right atrial abnormality (P pulmonale):** The P-wave amplitude in lead II is > 2.5 mm.
  - **Left atrial abnormality (P mitrale):** The P-wave width in lead II is > 120 msec, or terminal ⊖ deflection in V_1 is > 1 mm in amplitude and > 40 msec in duration. Notched P waves can frequently be seen in lead II.
- **Left ventricular hypertrophy (LVH;** see Figure 2.1-4):
  - **The amplitude of S in V_1 + R in V_5 or V_6 is > 35 mm.**
  - **Alternative criteria:** The amplitude of R in aVL + S in V_3 is > 28 mm in men or > 20 mm in women.
- **Right ventricular hypertrophy (RVH):** Right-axis deviation and an R wave in V_1 > 7 mm.

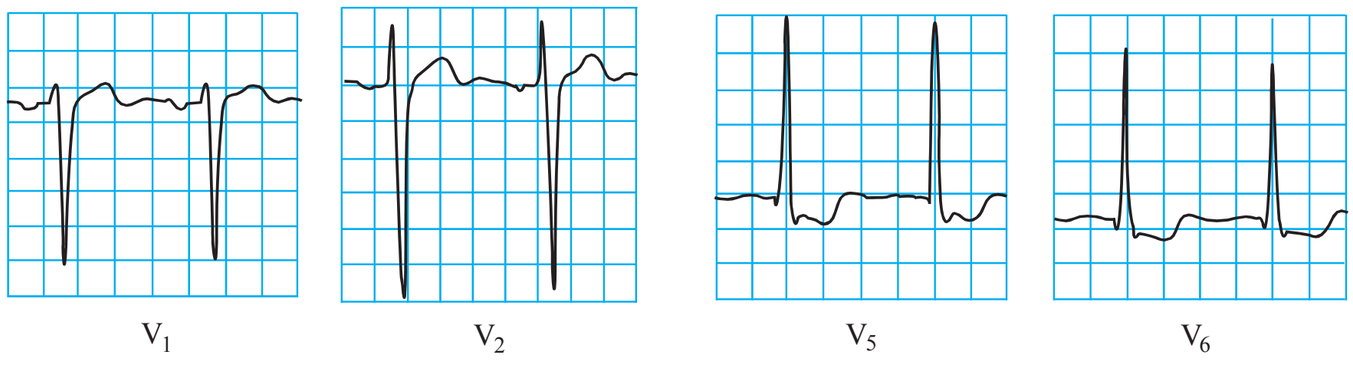


FIGURE 2.1-4. Left ventricular hypertrophy. Shown are leads V_1, V_2, V_5, and V_6. S wave in V_1 + R wave in V_5 = 45 mm. Note ST changes and T-wave inversion in V_5 and V_6, suggesting strain. (Reproduced with permission from Gomella LG, Haist SA. Clinician's Pocket Reference, 11th ed. New York, NY: McGraw-Hill; 2007.)

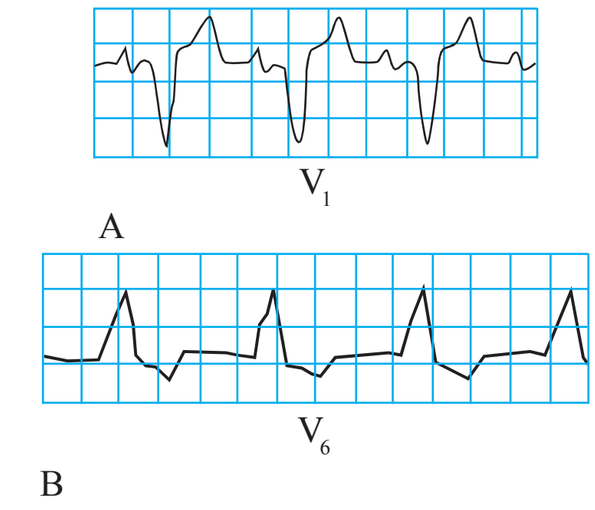


FIGURE 2.1-2. Left bundle branch block. Characteristic ECG findings are seen in leads V_1 **(A)** and V_6 **(B).** (Adapted with permission from USMLE-Rx.com.)

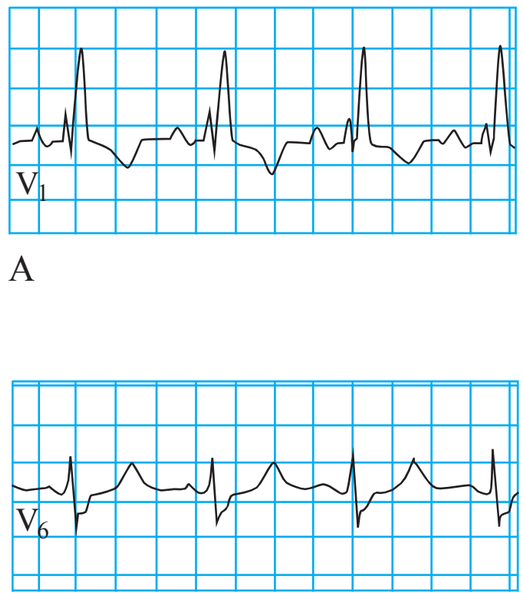


FIGURE 2.1-3. Right bundle branch block. Characteristic ECG findings are seen in leads V_1 **(A)** and V_6 **(B).** (Adapted with permission from USMLE-Rx.com.)

KEY FACT

P **P**ulmonale causes **P**eaked P waves.
P **M**itrale causes **M**-shaped P waves.

KEY FACT

Axis deviation can be a sign of ventricular enlargement.

Cardiac Physical Exam

Key examination findings that can narrow the differential include the following:

- **Jugular venous distention** (JVD, > 7 cm above the sternal angle): Most typically from **volume overload,** stemming from conditions such as right heart failure or pulmonary hypertension.
- **Hepatojugular reflux** (distention of neck veins upon applying pressure to the liver): Seen in same conditions as JVD.
- **Kussmaul sign (↑ in jugular venous pressure [JVP] with inspiration):** Often seen in **cardiac tamponade** and **constrictive pericarditis.**
- **Systolic murmurs** (see Table 2.1-2 and Figures 2.1-5 and 2.1-6).
  - **Aortic stenosis:** A **harsh systolic ejection** murmur that radiates to the carotids.
  - **Mitral regurgitation:** A **holosystolic** murmur that radiates to the axilla.
  - **Mitral valve prolapse:** A midsystolic or late systolic murmur with a **preceding click.**
  - **Flow murmur:** Usually a soft murmur that is position-dependent (very common, and does not imply cardiac disease).
- **Diastolic murmurs** (see Table 2.1-2 and Figures 2.1-5 and 2.1-6): Always abnormal.
  - **Aortic regurgitation:** An **early decrescendo** murmur.
  - **Mitral stenosis:** A **mid- to late, low-pitched** murmur.
- **Gallops:**
  - **S3 gallop:** A sign of fluid overload (ie, heart failure, mitral valve disease); often normal in younger patients and in high-output states (eg, pregnancy).
  - **S4 gallop:** A sign of decreased compliance (ie, hypertension, diastolic dysfunction); usually pathologic but can be normal in younger patients and in athletes.
- **Edema:**
  - **Pulmonary:** Left heart failure (fluid "backs up" into the lungs).
  - **Peripheral:** Right heart failure and biventricular failure (fluid "backs up" into the periphery). Also nephrotic syndrome, hepatic disease, lymphedema, hypoalbuminemia, and drugs.
- **Peripheral pulses:**
  - **Increased:** Compensated aortic regurgitation (bounding pulses); coarctation (greater in arms than legs); patent ductus arteriosus.
  - **Decreased:** Peripheral arterial disease; late-stage heart failure.
  - **Pulsus paradoxus** (↓ systolic BP with inspiration): **Pericardial tamponade;** also seen in obstructive lung diseases, tension pneumothorax, and foreign body in airway.
  - **Pulsus alternans** (alternating weak and strong pulses): Cardiac tamponade; impaired left ventricular systolic function. Poor prognosis.
  - **Pulsus parvus et tardus** (weak and delayed pulse): **Aortic stenosis.**

MNEMONIC

Heart auscultation locations:

All Physicians Take Money

Aortic
Pulmonic
Tricuspid
Mitral

TABLE 2.1-2. Cardiac Murmurs

Systolic Murmurs	Diastolic Murmurs
Aortic stenosis	Aortic regurgitation
Mitral regurgitation	Mitral stenosis
Mitral valve prolapse	
Tricuspid regurgitation	

Arrhythmias

BRADYARRHYTHMIAS AND CONDUCTION ABNORMALITIES

Table 2.1-3 outlines the etiologies, clinical presentation, and treatment of common bradyarrhythmias and conduction abnormalities.

TACHYARRHYTHMIAS

Tables 2.1-4 and 2.1-5 outline the etiologies, clinical presentation, and treatment of common supraventricular and ventricular tachyarrhythmias.

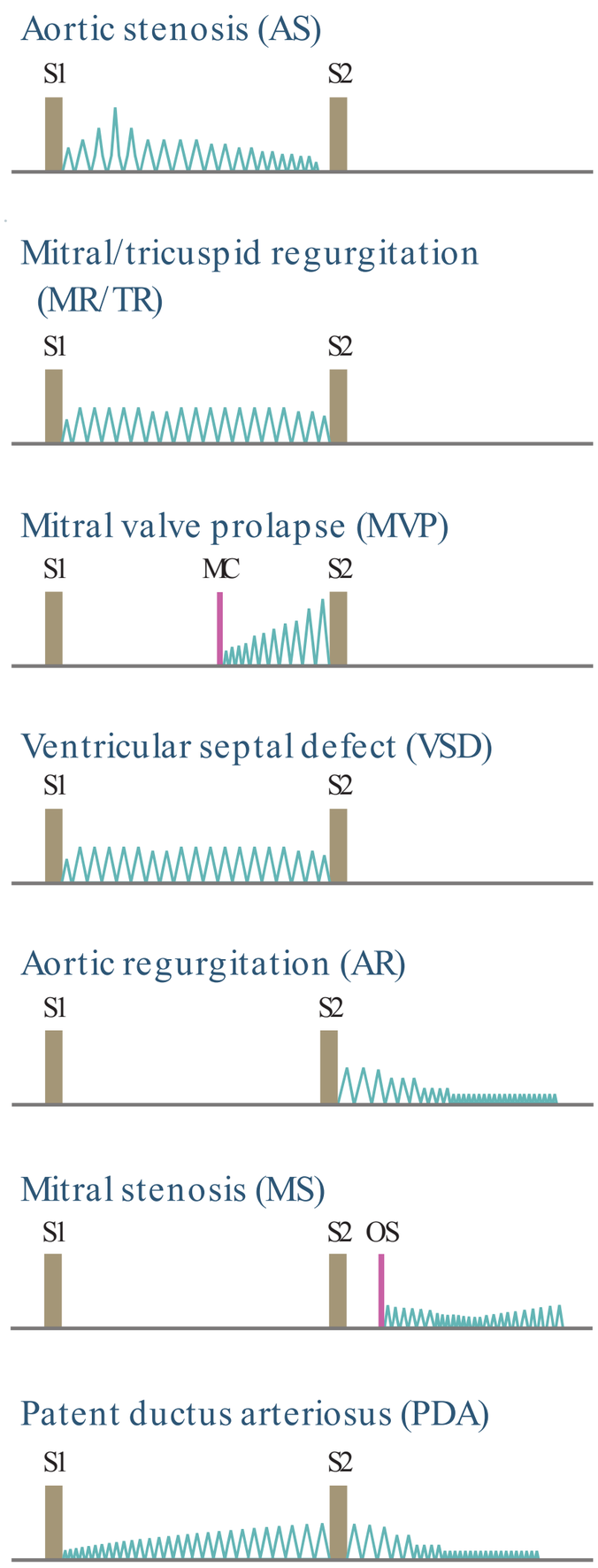


FIGURE 2.1-6. Heart murmurs. Visual representations of common heart murmurs are shown in relation to S1 and S2. MC = midsystolic click; OS = opening snap. (Systolic and diastolic figures adapted with permission from Le T et al. First Aid for the USMLE Step 1 2015. New York, NY: McGraw-Hill; 2015. Continuous figure adapted with permission from USMLE-Rx.com.)

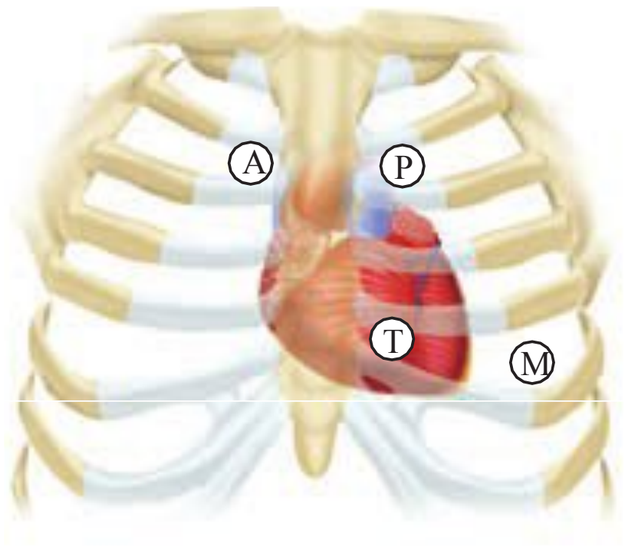


FIGURE 2.1-5. Auscultation locations. Auscultation sites are shown with associated valves. A = aortic valve; M = mitral valve; P = pulmonic valve; T = tricuspid valve. (Reproduced with permission from Le T et al. First Aid for the USMLE Step 1 2015. New York, NY: McGraw-Hill; 2015.)

MNEMONIC

Management options for atrial fibrillation—

ABCD

Anticoagulate
β-blockers to control rate
Cardiovert/**C**alcium channel blockers
Digoxin (in refractory cases)

KEY FACT

Use the **CHA_2DS_2-VASc** scoring system to estimate stroke risk in atrial fibrillation and anticoagulate for a score of 2 or more:

- **C**HF (1 point)
- **H**TN (1 point)
- **A**ge ≥ 75 (**2** points)
- **D**iabetes (1 point)
- **S**troke or TIA history (**2** points)
- **V**ascular disease (1 point)
- **A**ge 65–74 (1 point)
- **S**ex **c**ategory (female) (1 point)

Q

A college aged man "passed out" while playing basketball and had no prodromal symptoms or signs of seizure. His cardiac examination is unremarkable, and an ECG shows a slurred upstroke of the QRS. What are the next best steps?

TABLE 2.1-3. Bradyarrhythmias and Conduction Abnormalities

type	etiology	Signs/Symptoms	ecg Findings	treatment
Sinus bradycardia	Normal response to cardiovascular conditioning; can also result from sinus node dysfunction or from β-blocker or CCB excess.	May be asymptomatic, but may also present with lightheadedness, syncope, chest pain, or hypotension. 	Sinus rhythm. Ventricular rate < 60 bpm.	None if asymptomatic; atropine may be used to ↑ heart rate. Pacemaker placement is the definiti e treatment in severe cases.
First-degree AV block	Can occur in normal individuals; associated with ↑ vagal tone and with β-blocker or CCB use.	Asymptomatic. 	PR interval > 200 msec.	None necessary.
Second-degree AV block **(Mobitz type I/Wenckebach)**	Drug ef ects (digoxin, β-blockers, CCBs) or **↑ vagal tone;** right coronary ischemia or infarction.	Usually asymptomatic. 	Progressive PR lengthening until a dropped beat occurs; the PR interval then resets.	Stop the of ending drug. Atropine as clinically indicated.
Second-degree AV block **(Mobitz type II)**	Results from fib otic disease of the conduction system or from acute, subacute, or prior MI.	Occasionally syncope; **frequent progression to third-degree AV block.** 	Unexpected dropped beat(s) without a change in PR interval.	**Pacemaker placement.**
Third-degree AV block (complete)	No electrical communication between the atria and ventricles.	Syncope, dizziness, acute heart failure, hypotension, cannon A waves. 	No relationship between P waves and QRS complexes.	**Pacemaker placement.**
Sick sinus syndrome/ tachycardia-bradycardia syndrome	A heterogeneous disorder that leads to intermittent supraventricular tachyarrhythmias and bradyarrhythmias.	2° to tachycardia or bradycardia; may include syncope, palpitations, dyspnea, chest pain, TIA, and stroke.		**The most common indication for pacemaker placement.**

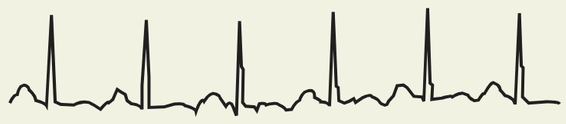
A

This is Wolff-Parkinson-White syndrome (WPW). Advise against vigorous physical activity, use procainamide for arrhythmias, and refer for an electrophysiology study.

Congestive Heart Failure

A clinical syndrome caused by inability of the heart to pump enough blood to maintain fluid and metabolic homeostasis. Risk factors include CAD, HTN, cardiomyopathy, valvular heart disease, and diabetes. The American Heart Association/American College of Cardiology guidelines classify heart failure according to clinical syndromes, but alternative classification systems,

TABLE 2.1-4. Supraventricular Tachyarrhythmias

type	etiology	Signs/Symptoms	ecg Findings	treatment
		atrial		
Sinus tachycardia	Normal physiologic response to fear, pain, and exercise. Can also be 2° to hyperthyroidism, volume contraction, infection, or PE.	Palpitations, shortness of breath. 	Sinus rhythm. Ventricular rate > 100 bpm.	Treat the underlying cause.
AF	**Acute AF—PIRATES:** **P**ulmonary disease **I**schemia **R**heumatic heart disease **A**nemia/**A**trial myxoma **T**hyrotoxicosis **E**thanol **S**epsis **Chronic AF**—HTN, CHF.	Often asymptomatic but may present with shortness of breath, chest pain, or palpitations. Physical examination reveals an **irregularly irregular pulse.** 	No discernible P waves, with variable and irregular QRS response.	For chronic AF, initial therapy: Rate control with β-blockers, CCBs, or digoxin. Anticoagulate with warfarin for patients with CHA_2DS_2-VASc score ≥ 2. For unstable AF, or new-onset AF (of < 2 days) cardiovert. If > 2 days or unclear duration, must get TEE to rule out atrial clot.
Atrial flutter	Circular movement of electrical activity around the atrium at a rate of approximately 300 times per minute.	Usually asymptomatic but can present with palpitations, syncope, and lightheadedness. 	Regular rhythm; **"sawtooth" appearance of P waves** can be seen. The atrial rate is usually 240–320 bpm and the ventricular rate ~ 150 bpm.	Anticoagulation, rate control, and cardioversion guidelines as in AF above.
Multifocal atrial tachycardia	Multiple atrial pacemakers or reentrant pathways; COPD, hypoxemia.	May be asymptomatic. At least **3 different P-wave morphologies.** 	Three or more unique P-wave morphologies; rate > 100 bpm.	Treat the underlying disorder; verapamil or β-blockers for rate control and suppression of atrial pacemakers (not very effective).

(continues)

TABLE 2.1-4. Supraventricular Tachyarrhythmias (continued)

type	etiology	Signs/Symptoms	ecg Findings	treatment
		aV junction		
AVNRT	A reentry circuit in the AV node depolarizes the atrium and ventricle nearly simultaneously.	Palpitations, shortness of breath, angina, syncope, lightheadedness.	Rate 150–250 bpm; **P wave is often buried** in QRS or shortly after.	Cardiovert if hemodynamically unstable. Carotid massage, Valsalva, or adenosine can stop the arrhythmia.
AVRT	An ectopic connection between the atrium and ventricle that causes a reentry circuit. Seen in WPW.	Palpitations, shortness of breath, angina, syncope, lightheadedness.	A retrograde P wave is often seen after a normal QRS. A **preexcitation delta wave is characteristically seen in WPW.**	Same as that for AVNRT.
Paroxysmal atrial tachycardia	Rapid ectopic pacemaker in the atrium (not sinus node).	Palpitations, shortness of breath, angina, syncope, lightheadedness.	Rate > 100 bpm; P wave with an unusual axis **before** each normal QRS.	Adenosine can be used to unmask underlying atrial activity by slowing down the rate.

KEY FACT

The most common cause of right-sided heart failure is left-sided heart failure.

including that of the New York Heart Association (NYHA), include functional severity, left-sided vs right-sided failure, and systolic vs nonsystolic failure (see Tables 2.1-6–2.1-8).

SYSTOLIC DYSFUNCTION

A ↓ **EF (< 50%)** and ↑ left ventricular end-diastolic volumes. It is caused by inadequate left ventricular contractility or ↑ afterload. The heart compensates for ↓ EF and ↑ preload through hypertrophy and ventricular dilation (Frank-Starling law), but the compensation ultimately fails, leading to ↑ myocardial work and worsening systolic function.

History/Pe

- **Exertional dyspnea is the earliest and most common presenting symptom** and progresses to orthopnea, paroxysmal nocturnal dyspnea (PND), and finally rest dyspnea.
- Patients may report chronic cough, fatigue, and peripheral edema.
- Examination reveals parasternal lift, an elevated and sustained left ventricular impulse, an S3/S4 gallop, JVD, and peripheral edema.
- Look for signs to distinguish left- from right-sided failure (see Table 2.1-7).

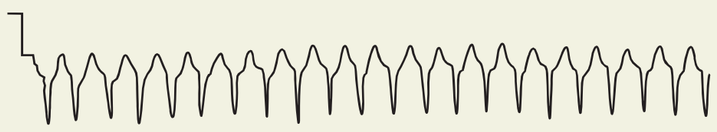
KEY FACT

Diuretics and digoxin are for symptomatic relief only and confer no mortality benefit.

Diagnosis

- **CHF is a clinical syndrome** whose diagnosis is based on signs and symptoms.
- Diagnostic studies that may support diagnosis include:
  - **CXR:** May show **cardiomegaly,** cephalization of pulmonary vessels,

TABLE 2.1-5. Ventricular Tachyarrhythmias

Type	Etiology	Signs/Symptoms	ECG Findings	Treatment
PVCs	Ectopic beats arise from ventricular foci. Associated with hypoxia, electrolyte abnormalities, and hyperthyroidism.	Usually asymptomatic but may lead to palpitations. 	Early, wide QRS not preceded by a P wave. PVCs are usually followed by a compensatory pause.	Treat the underlying cause. If symptomatic, give β-blockers or, occasionally, other antiarrhythmics.
WPW	Abnormal fast accessory pathway from atria to ventricle.	Palpitations, dyspnea, dizziness, and rarely cardiac death.	Characteristic delta wave with widened QRS complex and shortened PR interval (see Figure 2.1-7).	Observation for asymptomatic patients.
VT	Can be associated with CAD, MI, and structural heart disease.	Nonsustained VT (lasts < 30 seconds) is often asymptomatic; sustained VT (lasts > 30 seconds) can lead to palpitations, hypotension, angina, and syncope. Can progress to VF and death. 	Three or more consecutive PVCs; wide QRS complexes in a regular rapid rhythm; may see AV dissociation.	Cardioversion if unstable. Antiarrhythmics (eg, amiodarone, lidocaine, procainamide).
VF	Associated with CAD and structural heart disease. Also associated with cardiac arrest (together with asystole).	Syncope, absence of BP, no pulse. 	Totally erratic wide-complex tracing.	Immediate electrical defibrillation and ACLS protocol.
Torsades de pointes	Associated with long QT syndrome, proarrhythmic response to medications, hypokalemia, congenital deafness, and alcoholism.	Can present with sudden cardiac death; typically associated with palpitations, dizziness, and syncope. 	Polymorphous QRS; VT with rates between 150 and 250 bpm.	Give magnesium initially and cardiovert if unstable. Correct hypokalemia; withdraw of ending drugs.

pleural effusions, vascular congestion, **pulmonary edema,** and prominent hila (see Figure 2.1-8).

- **Echocardiogram:** ↓ EF and ventricular dilation, may help pinpoint underlying cause (ie, AF, old MI, or LVH).
- **Lab abnormalities: Brain natriuretic peptide > 500 pg/mL,** ↑ creatinine (sometimes), and ↓ sodium in later stages.

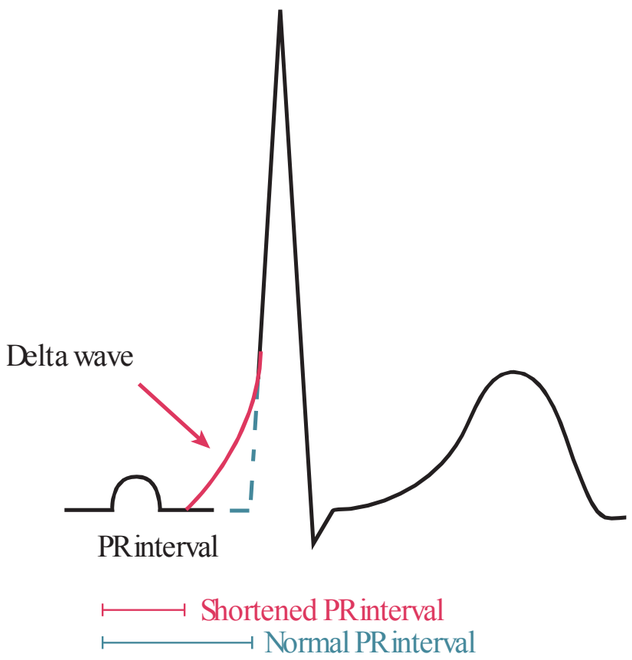


FIGURE 2.1-7. Ventricular tachyarrhythmias. Characteristic delta wave with widened QRS complex and shortened PR interval in WPW. (Reproduced with permission from Le T et al. First Aid for the USMLE Step 1 2015. New York, NY: McGraw-Hill; 2015.)

MNEMONIC

Acute CHF management—

LMNOP

Lasix (furosemide)
Morphine
Nitrates
Oxygen
Position (upright)

KEY FACT

Loops lose calcium; thiazides take it in.

TABLE 2.1-6. NYHA Functional Classification of CHF

Class	Description
I	**No limitation of activity;** no symptoms with normal activity.
II	Slight limitation of activity; comfortable at rest **or with mild exertion.**
III	Marked limitation of activity; **comfortable only at rest.**
IV	Any physical activity brings on discomfort; **symptoms present at rest.**

Treatment

- **Acute:**
  - **Pharmacologic therapy** (see Table 2.1-9):
    - Loop diuretics (most commonly) for **aggressive diuresis.**
    - ACEIs for patients who can tolerate (consider angiotensin receptor blockers [ARBs] for those who can't).
    - β-blockers should be avoided during decompensated CHF but should be restarted once patient is euvolemic.
  - Correct underlying causes such as arrhythmias, myocardial ischemia, and drugs (eg, CCBs, antiarrhythmics, NSAIDs, alcohol, thyroid and valvular disease, high-output states).
- Treat acute pulmonary congestion with **LMNOP** (see mnemonic).
- **Chronic:**
  - **Lifestyle:** Control comorbid conditions, and **limit dietary sodium and fluid intake.**
  - **Pharmacologic therapy:**
    - **β-blockers and ACEIs/ARBs:** Help prevent remodeling of the heart and ↓ mortality for NYHA class II–IV patients. Avoid CCBs (can worsen edema).
    - **Diuretics** (most commonly loop diuretics): Prevent volume overload.
    - Low-dose **spironolactone:** Shown to ↓ mortality risk in patients with NYHA class III–IV heart failure.
    - **Daily ASA and a statin** are recommended if the underlying cause is a prior MI.
  - **Advanced treatments:**
    - **Implantable cardiac defibrillator (ICD)** in patients with an EF < 35%.
    - **Left ventricular assist device (LVAD) or cardiac transplantation** may be necessary in patients who are unresponsive to maximal medical therapy.

TABLE 2.1-7. Left-Sided vs Right-Sided Heart Failure

Left-Sided CHF Symptoms	Right-Sided CHF Symptoms
Dyspnea predominates	**Fluid retention predominates**
Left-sided S3/S4 gallop	Right-sided S3/S4 gallop
Bilateral basilar rales	JVD
Pleural effusion	Hepatojugular reflux
Pulmonary edema	Peripheral edema
Orthopnea, paroxysmal nocturnal dyspnea	Hepatomegaly, ascites

TABLE 2.1-8. Comparison of Systolic and Diastolic Dysfunction

Variable	Systolic dysfunction	Nonsystolic dysfunction
Patient age	Often < 65 years of age.	Often > 65 years of age.
Comorbidities	Dilated cardiomyopathy, valvular heart disease.	Restrictive or hypertrophic cardiomyopathy; renal disease or HTN.
Physical examination	Displaced PMI, S3 gallop.	Sustained PMI, S4 gallop.
CXR	Pulmonary congestion, cardiomegaly.	Pulmonary congestion.
ECG/echocardiography	Q waves, ↓ EF (< 40%).	LVH, normal EF (> 55%).

NONSYSTOLIC DYSFUNCTION

Defined by ↓ **ventricular compliance with normal systolic function.** The ventricle has either impaired active relaxation (2° to ischemia, aging, and/or hypertrophy) or impaired passive filling (scarring from prior MI; restrictive cardiomyopathy). Left ventricular end-diastolic pressure ↑, cardiac output remains essentially normal, **and EF is normal or ↑.**

History/PE

Associated with stable and unstable angina, shortness of breath, dyspnea on exertion, arrhythmias, MI, heart failure, and sudden death.

Treatment

- Diuretics are first-line therapy (see Table 2.1-9).
- Maintain rate and BP control via β-blockers, ACEIs, ARBs, or CCBs.
- Digoxin is not useful in these patients.

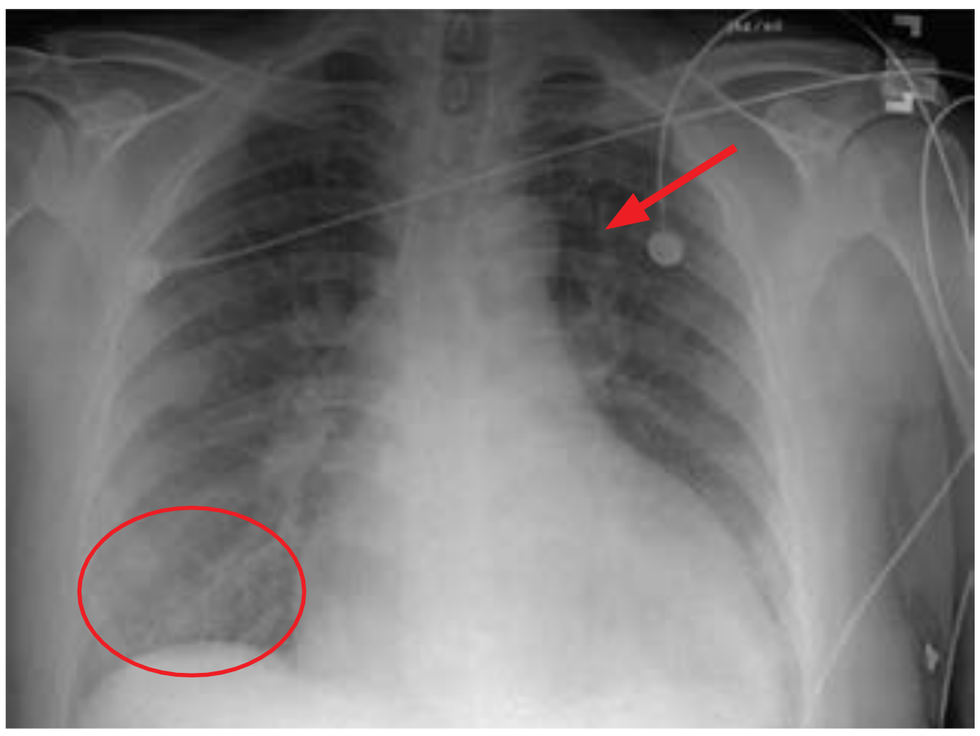


FIGURE 2.1-8. Chest x-ray film with evidence of congestive heart failure Frontal CXR demonstrates marked cardiomegaly, cephalization of vessels (arrow), interstitial edema (circle), and left-sided pleural effusion that raise concern for CHF. (Reproduced with permission from Tintinalli JE et al. Tintinalli's Emergency Medicine: A Comprehensive Study Guide, 7th ed. New York, NY: McGraw-Hill; 2011.)

Q 1

A man was admitted for a CHF exacerbation with low EF. The patient is now ready for discharge, and his medications include furosemide and metoprolol. Assuming no contraindications, what medication would be appropriate to add to his treatment regimen?

Q 2

A woman with HTN and prior MI has an examination notable for a displaced PMI, an S3, a nonelevated JVP, and bibasilar rales. What is the next best step in diagnosis?

TABLE 2.1-9. Types of Diuretics

Class	Examples	Side effects
Loop diuretics	**Furosemide,** ethacrynic acid, bumetanide, torsemide	Ototoxicity, **hypokalemia,** hypocalcemia, dehydration, gout.
Thiazide diuretics	**Hydrochlorothiazide,** chlorothiazide, chlorthalidone	Hypokalemic metabolic alkalosis, hyponatremia, and hyper**GLUC** (hyper**G**lycemia, hyper**L**ipidemia, hyper**U**ricemia, hyper**C**alcemia).
K^+-sparing agents	**Spironolactone,** triamterene, amiloride	Hyperkalemia, gynecomastia, sexual dysfunction.
Carbonic anhydrase inhibitors	Acetazolamide	Hyperchloremic metabolic acidosis, neuropathy, NH_3 toxicity, sulfa allergy.
Osmotic agents	Mannitol	Pulmonary edema, dehydration. Contraindicated in anuria and CHF.

Cardiomyopathy

Myocardial disease; categorized as dilated, hypertrophic, or restrictive (see Table 2.1-10 and Figure 2.1-9).

DILATED CARDIOMYOPATHY

The most common cardiomyopathy. **Left ventricular dilation and ↓ EF** must be present for diagnosis. Most cases are idiopathic, but known 2° causes include alcohol, myocarditis, postpartum status, drugs (**doxorubicin,** AZT, cocaine), endocrinopathies (thyroid dysfunction, acromegaly, pheochromocytoma), infection (**coxsackievirus,** HIV, **Chagas disease,** parasites), genetic fac-

TABLE 2.1-10. Differential Diagnosis of Cardiomyopathies

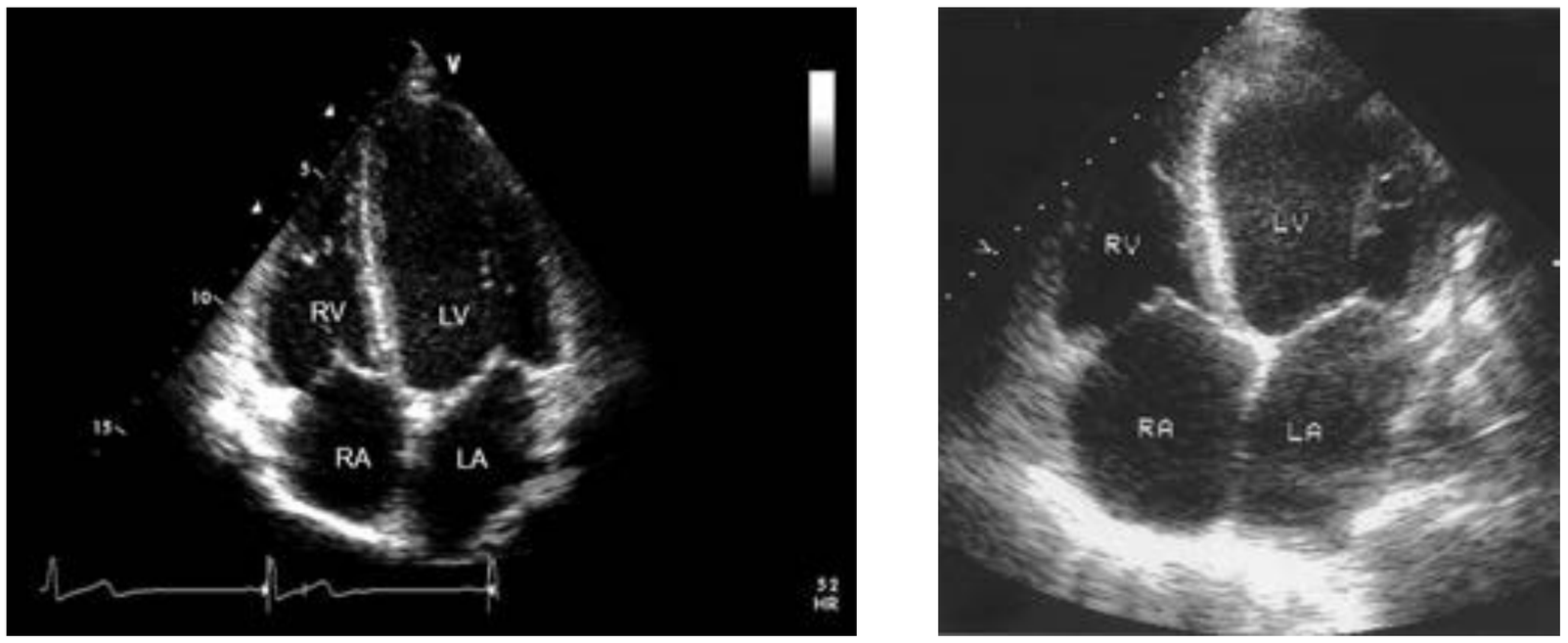
	Type		
Variable	dilated	hypertrophic	restrictive
Major abnormality	Impaired contractility	Impaired relaxation	Impaired elasticity
Left ventricular cavity size (end diastole)	↑↑	↓	↑
Left ventricular cavity size (end systole)	↑↑	↓↓	↑
EF	↓↓	↑ (or normal)	↓ (or normal)
Wall thickness	Usually ↓	↑↑	Usually ↑

1 A

Add an angiotensin-converting enzyme inhibitor (ACEI) to this patient's current regimen. ACEIs have been shown to have a ⊕ mortality benefit when used with β-blockers in NYHA class II–IV heart failure patients.

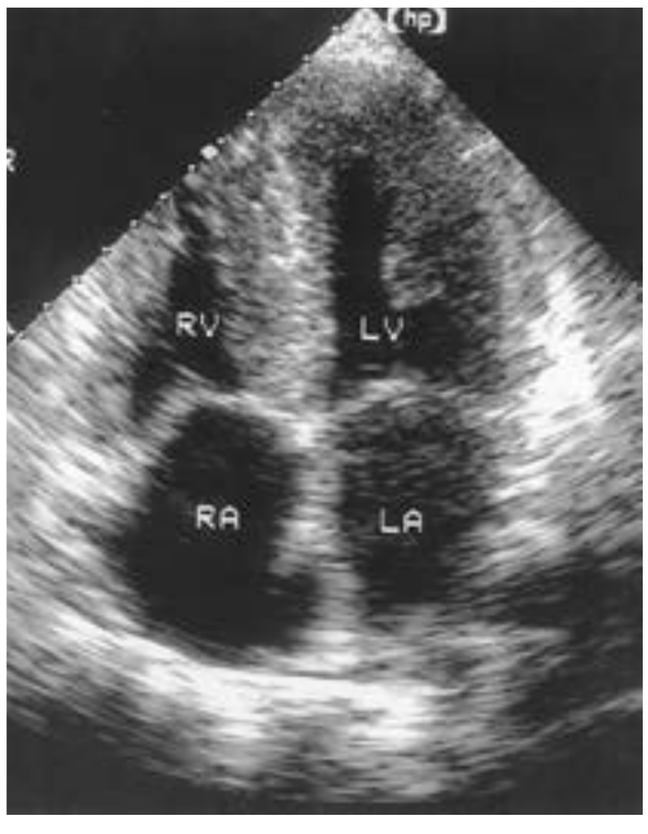
2 A

This patient has evidence of dilated cardiomyopathy. An echocardiogram would be the next best diagnostic step.



A

B



C

FIGURE 2.1-9. Cardiomyopathies. Echocardiogram four-chamber views of **(A)** a normal heart, **(B)** dilated cardiomyopathy, and **(C)** hypertrophic cardiomyopathy. (Reproduced with permission from Fuster Vet al. Hurst's The Heart, 12th ed. New York, NY: McGraw-Hill; 2008.)

tors, and nutritional disorders (wet beriberi). The most common causes of 2° dilated cardiomyopathy are ischemia and long-standing hypertension.

History/Pe

- Often presents with gradual development of CHF symptoms.
- Examination often reveals displacement of the left ventricular impulse, JVD, an S3/S4 gallop, or mitral/tricuspid regurgitation.

Diagnosis

- **Echocardiography is diagnostic.**
- CXR shows an enlarged, balloonlike heart and pulmonary congestion.

Treatment

- Address the underlying etiology (eg, alcohol use, endocrine disorders).
- Treat CHF as noted in above section with lifestyle changes, and pharmacologic and advanced treatments.

KEY FACT

An S3 gallop signifies rapid ventricular filling in the setting of fluid overload and is associated with dilated cardiomyopathy.

KEY FACT

An S4 gallop signifies a stiff, noncompliant ventricle and ↑ "atrial kick," and may be associated with hypertrophic cardiomyopathy.

HYPERTROPHIC CARDIOMYOPATHY

KEY FACT

HOCM is the most common cause of sudden death in young, healthy athletes in the United States.

Impaired left ventricular relaxation and filling (nonsystolic dysfunction) due to thickened ventricular walls. Hypertrophy frequently involves the interventricular septum, leading to left ventricular outflow tract obstruction and impaired ejection of blood. The congenital form, hypertrophic obstructive cardiomyopathy (HOCM), is **inherited as an autosomal dominant trait** in 50% of HOCM patients and is the most common cause of sudden death in young, healthy athletes in the United States. Other causes of marked hypertrophy include HTN and aortic stenosis.

History/PE

- Patients are often asymptomatic but may also present with syncope, dyspnea, palpitations, angina, or sudden cardiac death.
- Key finding is **a systolic ejection crescendo-decrescendo murmur that ↑ with ↓ preload** (eg, Valsalva maneuver, standing) and ↓ with ↑ preload (eg, passive leg raise). Examination also often reveals a sustained apical impulse, and an S4 gallop.

Diagnosis

- **Echocardiography is diagnostic** and shows an asymmetrically thickened septum and dynamic obstruction of blood flow.
- ECG may show signs of LVH.
- CXR may reveal left atrial enlargement (LAE) 2° to mitral regurgitation.

Treatment

- β-blockers are initial therapy for symptomatic relief; CCBs are second-line agents.
- Surgical options for HOCM with persistent symptoms include partial excision or alcohol ablation of the myocardial septum.
- Patients should avoid intense athletic competition and training.

RESTRICTIVE CARDIOMYOPATHY

Decreased elasticity of myocardium leading to impaired diastolic filling without significant systolic dysfunction (a normal or near-normal EF). It is **caused by infiltrative disease** (amyloidosis, sarcoidosis, hemochromatosis) or by scarring and fibrosis (2° to radiation).

History/PE

Signs and symptoms of left-sided and right-sided heart failure occur, but symptoms of right-sided heart failure (JVD, peripheral edema) often predominate.

Diagnosis

- **Echocardiography is key for diagnosis,** with rapid early filling and a near-normal EF. CXR, MRI, and cardiac catheterization are helpful for characterization (eg, sarcoid, amyloidosis).
- Cardiac biopsy may reveal fibrosis or evidence of infiltration.
- ECG frequently shows LBBB; low voltages are seen in amyloidosis.

Treatment

Therapeutic options are limited and are generally palliative only. Medical treatment includes cautious use of diuretics for fluid overload and vasodilators to ↓ filling pressure.

Coronary Artery Disease

Clinical manifestations include stable and unstable angina, shortness of breath, dyspnea on exertion, arrhythmias, MI, heart failure, and sudden death.

- **Risk factors include:**
  - Diabetes mellitus (DM)
  - Family history of premature CAD (males < 55, females < 65)
  - Smoking
  - Dyslipidemia
  - Abdominal obesity
  - HTN
  - Age (males > 45, females > 55)
  - Male gender

CAD risk equivalents include DM, symptomatic carotid artery disease, peripheral arterial disease, and abdominal aortic aneurysm (AAA).

KEY FACT

Major risk factors for CAD include age, male gender, ↑ LDL, ↓ HDL, HTN, a family history, and smoking.

ANGINA PECTORIS

Substernal chest pain 2° to myocardial ischemia (O_2 supply-and-demand mismatch). Prinzmetal (variant) angina mimics angina pectoris but is caused by vasospasm of coronary vessels. It classically affects young women at rest in the early morning and is associated with ST-segment elevation in the absence of cardiac enzyme elevation.

History/Pe

- The **classic triad** consists of **substernal chest pain** that is usually **precipitated by stress** or exertion and is **relieved by rest** or nitrates.
- Pain can radiate to neck or arm and may be associated with shortness of breath, nausea/vomiting, diaphoresis, or lightheadedness.
- Pain is usually described as dull and pressure-like.

KEY FACT

Pain that is sharp or stabbing, or that changes with position, breathing, or touch is less likely to be ischemic.

Diagnosis

- **ECG** is the best initial test for any type of chest pain.
- **Stress testing:** ST-segment or wall-motion changes with exercise or pharmacologic stress are diagnostic of CAD. ECG stress test is contraindicated for patients with abnormal baseline ECGs. (Note: Do not perform stress tests on asymptomatic patients with low pretest probability of disease.)
- Rule out pulmonary, GI, or other cardiac causes of chest pain.

noncardiac Differential Diagnosis

- **GERD:** History described as hoarseness and worse after meals; relief of symptoms with proton pump inhibitors confirms diagnosis.
- **Musculoskeletal/costochondritis:** Pain is described as tender to palpation and movement.
- **Pneumonia/pleuritis:** Pain is described as worsening with breathing (pleuritic).
- **Anxiety:** Patients may have history of panic disorder or anxiety attacks.

KEY FACT

Common causes of chest pain include GERD, angina, esophageal pain, musculoskeletal disorders (costochondritis, trauma), and pneumonia.

KEY FACT

Only ASA and β-blockers have been shown to have a mortality benefit in the treatment of angina.

Treatment

- Treatment for chronic stable angina includes **ASA, β-blockers,** and **nitroglycerin.**
- Initiate risk factor reduction (eg, smoking, cholesterol, HTN). Hormone replacement therapy is not protective in postmenopausal women.

Acute Coronary Syndromes

A spectrum of clinical syndromes caused by plaque disruption or vasospasm that leads to acute myocardial ischemia.

UNSTABLE ANGINA/NON-ST-ELEVATION MYOCARDIAL INFARCTION

KEY FACT

U Ain't got enzymes with **U**nstable **A**ngina.

Unstable angina is defined as chest pain that is (1) **new onset,** is (2) **accelerating** (ie, occurs with less exertion, lasts longer, or is less responsive to medications), or (3) **occurs at rest;** it is distinguished from stable angina pectoris by patient history. It signals the presence of possible **impending infarction** based on plaque instability. In contrast, **NSTEMI** indicates myocardial necrosis marked by elevations in **troponin I and creatine kinase–MB isoenzyme (CK-MB)** without ST-segment elevations seen on ECG.

Diagnosis

- Patients should be risk stratified according to the Thrombolysis in Myocardial Infarction (TIMI) study criteria (see Table 2.1-11).
- Unstable angina is not associated with elevated cardiac markers, but ST changes may be seen on ECG.
- NSTEMI is diagnosed by serial cardiac enzymes and ECG.

Treatment

- Treat acute symptoms with ASA, O_2, IV nitroglycerin, and IV morphine, and consider β-blockers as hemodynamics allow.

TABLE 2.1-11. TIMI Risk Score for Unstable Angina/NSTEMI

Characteristics	Point
History	
Age ≥ 65 years	1
Three or more CAD risk factors (premature family history, DM, smoking, HTN, ↑ cholesterol)	1
Known CAD (stenosis > 50%)	1
ASA use in past 7 days	1
Presentation	
Severe angina (2 or more episodes within 24 hours)	1
ST deviation ≥ 0.5 mm	1
+ cardiac marker	1
Risk score—total points[a]	(0–7)

[a]Patients at higher risk (risk score ≥ 3) benefit more from enoxaparin (vs unfractionated heparin), glycoprotein IIb/IIIa inhibitors, and early angiography.

- Admit to the hospital, and monitor until acute MI has been ruled out by serial cardiac enzymes.
- Patients with chest pain refractory to medical therapy, a TIMI score of ≥ 3, a troponin elevation, or ST changes > 1 mm should be given IV heparin and scheduled for angiography and possible revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG]).

ST-ELEVATION MYOCARDIAL INFARCTION

ST-segment elevations and cardiac enzyme release 2° to prolonged cardiac ischemia and necrosis.

History/Pe

- **Presentation: Acute-onset substernal chest pain,** commonly described as a pressure or tightness that can radiate to the left arm, neck, or jaw.
- **Associated symptoms:** Diaphoresis, shortness of breath, lightheadedness, anxiety, nausea/vomiting, and syncope.
- **Physical examination:** May reveal arrhythmias, hypotension (cardiogenic shock), and evidence of new CHF.
- **The best predictor of survival is left ventricular EF.**

Diagnosis

- **ECG** will show ST-segment elevations or new LBBB. ST-segment depressions and dominant R waves in leads V_1–V_2 can also be reciprocal change indicating posterior wall infarct.
- **Sequence of ECG changes:** Peaked T waves → ST-segment elevation → Q waves → T-wave inversion → ST-segment normalization → T-wave normalization over several hours to days.
- **Cardiac enzymes:**
  - **Troponin I** is the most sensitive and specific cardiac enzyme.
  - **CK-MB** and the CK-MB/total CK ratio (CK index) are also regularly checked.
  - Both troponin I and CK-MB can take up to 6 hours to rise following the onset of chest pain (see Figure 2.1-10).

MNEMONIC

When your patient is MOANing from an MI, remember—

MOAN

Morphine
Oxygen (to maintain saturations)
ASA
Nitrogen

KEY FACT

Women, diabetics, the elderly, and post–heart transplant patients may have atypical or clinically silent MIs.

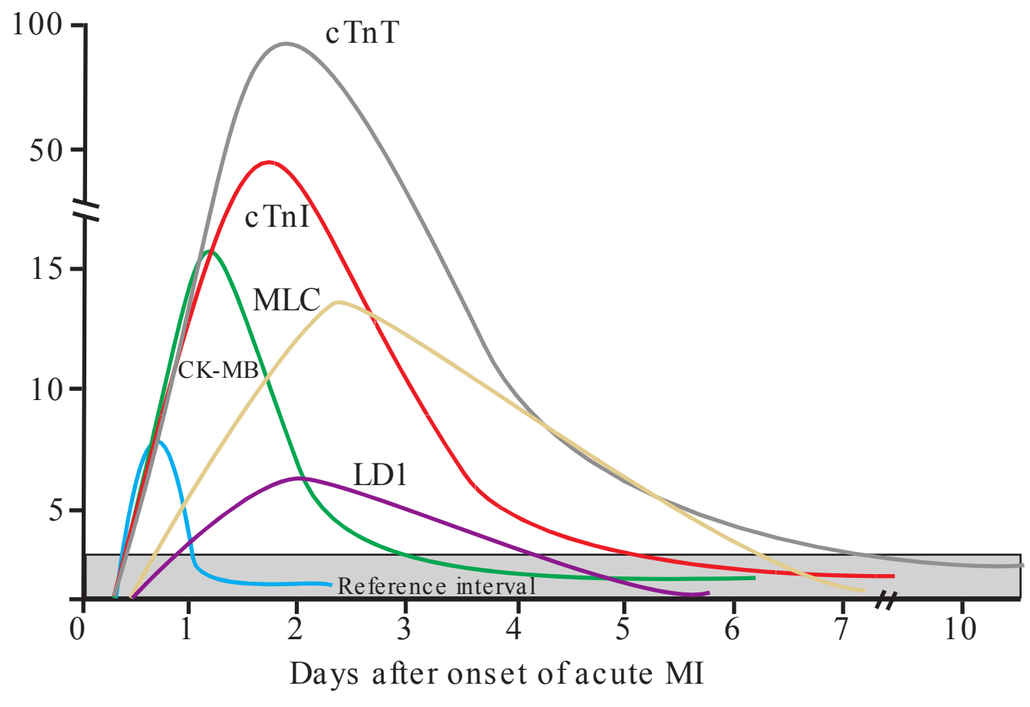


FIGURE 2.1-10. Typical pattern of serum marker elevation after an acute myocardial infarction. CK-MB = creatine kinase, MB isoenzyme; cTnI = cardiac troponin I; cTnT = cardiac troponin T; LD1 = lactate dehydrogenase isoenzyme 1; MLC = myosin light chain.
(Reproduced with permission from Tintinalli JE et al. Tintinalli's Emergency Medicine: A Comprehensive Study Guide, 6th ed. New York, NY: McGraw-Hill; 2004.)

- **ST-segment abnormalities:**
  - **Inferior MI** (involving the RCA/PDA): ST-segment elevation in leads **II, III,** and **aVF** (see Figure 2.1-11). Obtain a right-sided ECG to look for ST elevations in the right ventricle.
  - **Anterior MI** (involving LAD and diagonal branches): ST-segment elevation in leads $\mathbf{V_1}$–$\mathbf{V_4}$ (see Figure 2.1-12).
  - **Lateral MI** (involving LCA): ST-segment elevation in leads **I, aVL,** and $\mathbf{V_5}$–$\mathbf{V_6}$.
  - **Posterior MI:** ST-segment depression in leads $\mathbf{V_1}$–$\mathbf{V_2}$ (anterior leads) can be indicative. Obtain posterior ECG leads $\mathbf{V_7}$–$\mathbf{V_9}$ to assess for ST-segment elevations.

Treatment

- **Initial treatment:**
  - **Key medications:** ASA, β-blockers, clopidogrel, morphine, nitrates, and O_2.
  - If the patient is in heart failure or in cardiogenic shock, do not give β-blockers; instead, give ACEIs provided that the patient is not hypotensive.
  - In inferior wall MI, avoid nitrates due to risk of severe hypotension.
- **Interventions:**
  - **Emergent angiography and PCI** should be performed if possible.
  - If PCI cannot be performed within 90 minutes, **and** there are no contraindications to thrombolysis (eg, a history of hemorrhagic stroke or recent ischemic stroke, severe heart failure, or cardiogenic shock), **and** the patient presents within 3 hours of chest pain onset, thrombolysis with tPA, reteplase, or streptokinase should be performed instead of PCI.
- Long-term treatment includes ASA, ACEIs, β-blockers, high-dose statins (goal LDL < 100 mg/dL), and clopidogrel (if PCI was performed). Modify risk factors with dietary changes, exercise, and tobacco cessation.

KEY FACT

Indications for CABG:
- Unable to perform PCI (diffuse disease)
- Left main coronary artery disease
- Triple-vessel disease
- Depressed ventricular function

Complications

- **Arrhythmia** is the most common complication and most common cause of death following acute MI.

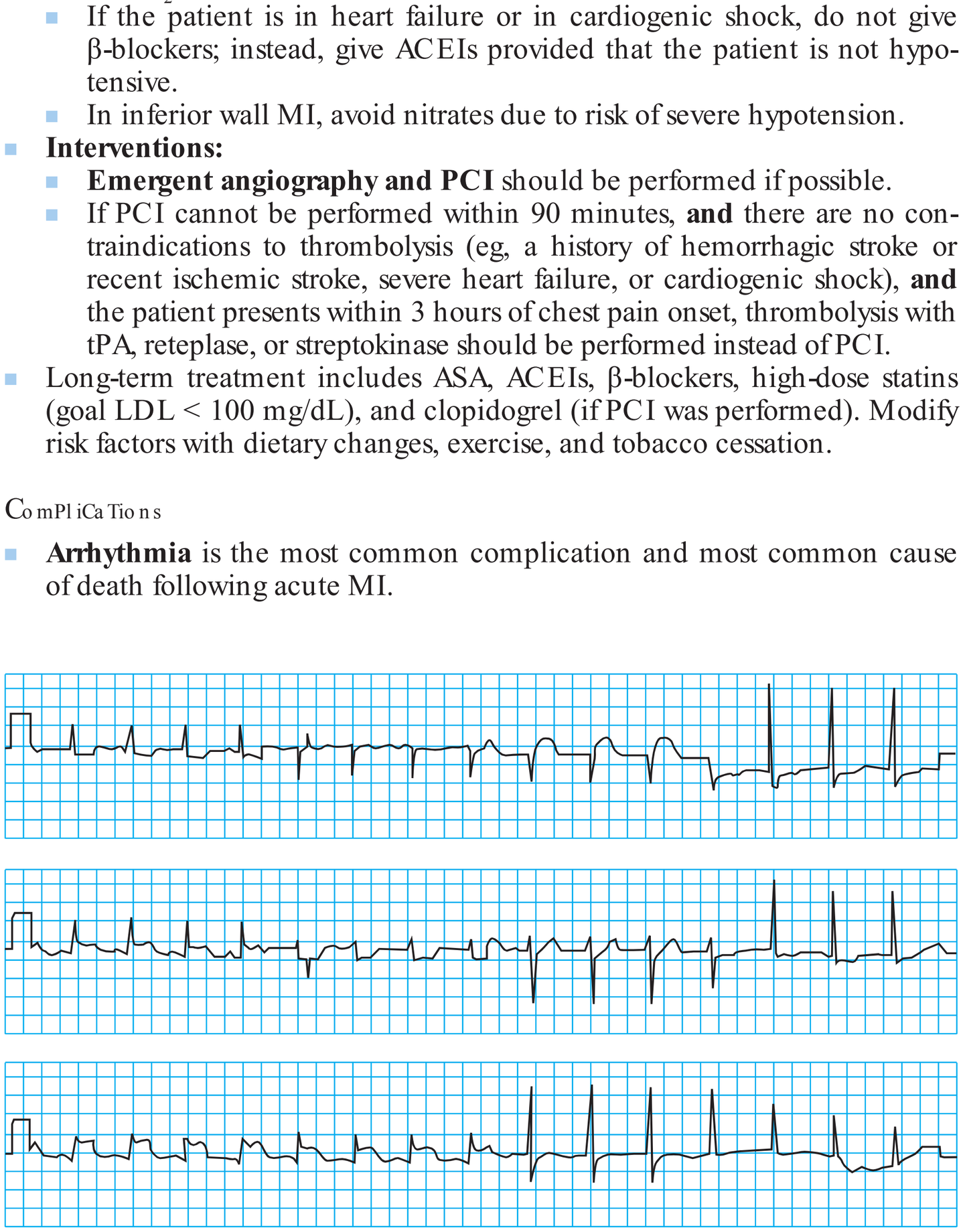


FIGURE 2.1-11. Inferior wall myocardial infarction. In this patient with acute chest pain, the ECG demonstrated acute ST-segment elevation in leads II, III, and aVF with reciprocal ST-segment depression and T-wave flattening in leads I, aVL, and V_4–V_6.



FIGURE 2.1-12. Anterior wall myocardial infarction. This patient presented with acute chest pain. The ECG showed acute ST-segment elevation in leads aVL and V_1–V_6, and hyperacute T waves.

- Less common complications include reinfarction, left ventricular wall rupture, VSD, pericarditis, papillary muscle rupture (with mitral regurgitation), left ventricular aneurysm or pseudoaneurysm, and mural thrombi.
- A timeline of common post-MI complications:
  - **First day:** Heart failure.
  - **2–4 days:** Arrhythmia, pericarditis.
  - **5–10 days:** Left ventricular wall rupture (acute pericardial tamponade causing electrical alternans, pulseless electrical activity), papillary muscle rupture (severe mitral regurgitation).
  - **Weeks to months:** Ventricular aneurysm (CHF, arrhythmia, persistent ST-segment elevation, mitral regurgitation, thrombus formation).
- **Dressler syndrome,** an autoimmune process occurring 2–10 weeks post-MI, presents with fever, pericarditis, pleural effusion, leukocytosis, and ↑ ESR.

Dyslipidemia

Total cholesterol level > 200 mg/dL, LDL > 130 mg/dL, triglycerides > 150 mg/dL, and HDL < 40 mg/dL, all of which are risk factors for CAD. Etiologies include obesity, DM, alcoholism, hypothyroidism, nephrotic syndrome, hepatic disease, Cushing syndrome, OCP use, high-dose diuretic use, and familial hypercholesterolemia.

History/Pe

- Most patients have **no specific signs or symptoms.**
- Patients with extremely high triglyceride or LDL levels may have xanthomas (eruptive nodules in the skin over the tendons), xanthelasmas (yellow fatty deposits in the skin around the eyes), and lipemia retinalis (creamy appearance of retinal vessels).

Diagnosis

- Conduct a fasting lipid profile for **patients > 35 years** of age or in those ≥ 20 years of age with CAD risk factors, and repeat **every 5 years** or sooner if lipid levels are elevated.

- Total serum cholesterol > 200 mg/dL on two different occasions is diagnostic of hypercholesterolemia.
- LDL > 130 mg/dL or HDL < 40 mg/dL is diagnostic of dyslipidemia even if total serum cholesterol is < 200 mg/dL.

Treatment

- Based on risk stratification using one of many cardiovascular risk calculators.
- The American College of Cardiology/American Heart Association recommends:
  - For patients with history of CAD, CVA, or PAD → **high-intensity statin.**
  - For patients with LDL between 70 and 189 mg/dL without diabetes:
    - ≥ 7.5% 10-year risk → **high-intensity statin.**
    - Between 5% and 7.5% 10-year → **moderate-intensity statin.**
    - ≤ 5% 10-year risk → **no statin.**
  - For patients with LDL between 70 and 189 mg/dL with diabetes:
    - ≥ 7.5% 10-year risk → **high-intensity statin.**
    - ≤ 7.5% 10-year → **moderate-intensity statin.**
  - For patients with LDL ≥ 190 mg/dL → **high-intensity statin.**
  - High-intensity therapy is defined as a goal reduction in LDL of > 50%, moderate-intensity as lowering by 30–50% or by specific medication and dosing guidelines (ie, atorvastatin 80 mg).
- As you cannot calculate the patient's risk on the USMLE, focus on obvious signs of elevated risk (smoking, diabetes) or decreased risk (young, healthy) when deciding if statin therapy is appropriate.
- The **first intervention** should be a **12-week trial of diet and exercise** in a patient with no known atherosclerotic vascular disease. Commonly used lipid-lowering agents are listed in Table 2.1-12.

KEY FACT

Dyslipidemia:
- LDL > 130 mg/dL or
- HDL < 40 mg/dL

TABLE 2.1-12. Lipid-Lowering Agents

Class	Examples	Effect on lipid profile	Side effects
HMG-CoA reductase inhibitors (statins)	Atorvastatin, simvastatin, lovastatin, pravastatin, rosuvastatin	↓ LDL, ↓ triglycerides	↑ LFTs, myositis, warfarin potentiation.
Lipoprotein lipase stimulators (fibrates)	Gemfibrozil	↓ triglycerides, ↑ HDL	GI upset, cholelithiasis, myositis, ↑ LFTs.
Cholesterol absorption inhibitors	Ezetimibe	↓ LDL	Diarrhea, abdominal pain. Can cause angioedema.
Niacin	Niaspan	↑ HDL, ↓ LDL	Skin flushing (can be prevented with ASA), paresthesias, pruritus, GI upset, ↑ LFTs.
Bile acid resins	Cholestyramine, colestipol, colesevelam	↓ LDL	Constipation, GI upset, LFT abnormalities, myalgias. Can ↓ absorption of other drugs from the small intestine.

Hypertension

A systolic BP > 140 mm Hg and/or a diastolic BP > 90 mm Hg based on three measurements separated in time in patients < 60 years (see Table 2.1-13). For patients ≥ 60 years without chronic kidney disease (CKD) or diabetes, HTN is defined as BP > 150 mm Hg and/or a diastolic BP > 90 mm Hg. Classified as 1° or 2°.

1° (ESSENTIAL) HYPERTENSION

Hypertension with no identifiable cause. Represents 95% of cases of HTN. Risk factors include a family history of HTN or heart disease, a high-sodium diet, smoking, obesity, ethnicity (blacks > whites), and advanced age.

History/Pe

- HTN is asymptomatic until complications develop.
- Patients should be evaluated for end-organ damage to the brain (stroke, dementia), eye (cotton-wool exudates, hemorrhage), heart (LVH), and kidney (proteinuria, CKD). Renal bruits may signify renal artery stenosis as the cause of HTN.

Diagnosis

Obtain a urinalysis, BUN/creatinine, and electrolytes to assess the extent of end-organ damage and possible 2° causes.

Treatment

- Begin with **lifestyle** modifications (weight loss, exercise, and diet improvement, including decreased alcohol and salt intake).
- The **BP goals** vary by age and comorbidities.
- Diuretics, CCBs, ACEIs, and β-blockers have been shown to ↓ mortality in uncomplicated HTN. They are first-line agents unless a comorbid condition requires another medication (see Table 2.1-14).
- Periodically test for end-organ complications, including renal complications (BUN, creatinine, urine protein-to-creatinine ratio) and cardiac complications (ECG evidence of hypertrophy).

TABLE 2.1-13. JNC8 Classification and Management of Hypertension

Patient Population	Initiate Treatment at:	Treat to Goal of:
Patients ≥ 60 years	SBP ≥ 150 mm Hg DBP ≥ 90 mm Hg	SBP ≤ 150 mm Hg DBP ≤ 90 mm Hg
Patients ≤ 60 years	SBP ≥ 140 mm Hg DBP ≥ 90 mm Hg	SBP ≤ 140 mm Hg DBP ≤ 90 mm Hg
Patients ≥ 18 years with CKD or diabetes	SBP ≥ 140 mm Hg DBP ≥ 90 mm Hg	SBP ≤ 140 mm Hg DBP ≤ 90 mm Hg

MNEMONIC

Treatment of HTN—

ABCD

ACEIs/**A**RBs
β-blockers
CCBs
Diuretics (typically thiazide diuretics)

Q 1

A woman is found with pulseless electrical activity on hospital day 7 after suffering a lateral wall STEMI. The ACLS protocol is initiated. What is the next best step?

Q 2

A 40-year-old man presents for a routine examination. His examination is significant for a BP of 145/75 mm Hg but is otherwise unremarkable, as are his lab results. What is the next best step?

TABLE 2.1-14. Treatment of 1° Hypertension in Specific Populations

Population	Agents
Uncomplicated	Diuretics, CCBs, ACEIs
CHF	Diuretics, β-blockers, **ACEIs,** ARBs, aldosterone antagonists
Diabetes	Diuretics, β-blockers, **ACEIs, ARBs,** CCBs
Post-MI	**β-blockers,** ACEIs, ARBs, aldosterone antagonists
Chronic kidney disease	**ACEIs, ARBs**
BPH	Diuretics, α_1-adrenergic blockers
Isolated systolic HTN	Diuretics, ACEIs, CCBs (dihydropyridines)
Pregnancy	β-blockers (typically labetalol), hydralazine

MNEMONIC

Causes of 2° hypertension—

CHAPS

Cushing syndrome
Hyperaldosteronism (Conn syndrome)
Aortic coarctation
Pheochromocytoma
Stenosis of renal arteries

KEY FACT

Hypertensive emergencies are diagnosed on the basis of the extent of end-organ damage, not BP measurement.

1 A

This patient has probably suffered a left ventricular free-wall rupture with acute cardiac tamponade. Emergent pericardiocentesis is the next best therapeutic and diagnostic step.

2 A

With a single BP recording and no evidence of end-organ damage, the next best step should consist of a repeat BP measurement at the end of the examination with a return visit if BP is still high.

2° HYPERTENSION

Hypertension 2° to an identifiable organic cause. See Table 2.1-15 for the diagnosis and treatment of common causes.

HYPERTENSIVE CRISES

A spectrum of clinical presentations in which elevated BPs (usually > 180/120 mm Hg) lead to end-organ damage.

History/Pe

Present with end-organ damage revealed by acute kidney injury, chest pain (ischemia or MI), back pain (aortic dissection), or changes in mental status (hypertensive encephalopathy).

Diagnosis

- **Hypertensive urgency:** Elevated BP with **mild to moderate symptoms (headache, chest pain) without end-organ damage.**
- **Hypertensive emergency:** Elevated BP with **signs or symptoms of impending end-organ damage** such as acute kidney injury, intracranial hemorrhage, papilledema, or ECG changes suggestive of ischemia or pulmonary edema.

Treatment

- **Hypertensive urgencies:** Can be treated with oral antihypertensives (eg, β-blockers, clonidine, ACEIs) with the goal of gradually lowering BP over 24–48 hours (see Table 2.1-16).
- **Hypertensive emergencies:** Treat with IV medications (labetalol, nitroprusside, nicardipine) with the goal of lowering mean arterial pressure by no more than 25% over the first 2 hours to prevent cerebral hypoperfusion or coronary insufficiency.

TABLE 2.1-15. Common Causes of 2° Hypertension

Etiology	Description	Management
1° renal disease	Often unilateral renal parenchymal disease.	Treat with ACEIs, which slow the progression of renal disease.
Renal artery stenosis	Especially common in patients < 25 and > 50 years of age with recent-onset HTN. Etiologies include fibromuscular dysplasia (younger patients) and atherosclerosis (older patients).	Diagnose with MRA or renal artery Doppler ultrasound. May be treated with angioplasty or stenting. Consider ACEIs in unilateral disease. (In bilateral disease, ACEIs can accelerate kidney failure by preferential vasodilation of the efferent arteriole.) Open surgery is a second option if angioplasty is not effective or feasible.
OCP use	Common in women > 35 years of age, obese women, and those with long-standing use.	Discontinue OCPs (effect may be delayed).
Pheochromocytoma	An adrenal gland tumor that secretes epinephrine and norepinephrine, leading to **episodic headache, sweating, and tachycardia.**	Diagnose with urinary metanephrines and catecholamine levels or plasma metanephrine. Surgical removal of tumor after **treatment with both α-blockers and β-blockers.**
Conn syndrome (hyperaldosteronism)	Most often 2° to an aldosterone-producing adrenal adenoma. Causes the **triad of HTN, unexplained hypokalemia, and metabolic alkalosis.**	Metabolic workup with plasma aldosterone and renin level; ↑ aldosterone and ↓ renin levels suggest 1° hyperaldosteronism. Surgical removal of tumor.
Cushing syndrome	Due to an ACTH-producing pituitary tumor, an ectopic ACTH-secreting tumor, or cortisol secretion by an adrenal adenoma or carcinoma. Also due to exogenous steroid exposure. (See the Endocrinology chapter for more details.)	Surgical removal of tumor; removal of exogenous steroids.
Coarctation of the aorta	See the Pediatrics chapter.	Surgical repair.

Pericardial Disease

Results from acute or chronic pericardial insults; may lead to pericardial effusion.

PERICARDITIS

Inflammation of the pericardial sac. It can compromise cardiac output via tamponade or constrictive pericarditis. Most commonly idiopathic, although known etiologies include viral infection, TB, SLE, uremia, drugs, radiation, and neoplasms. May also occur after MI (either within days after MI or as a delayed phenomenon; ie, Dressler syndrome) or open-heart surgery (see Figure 2-1-13).

History/Pe

- **Presentation:** Pleuritic chest pain, dyspnea, cough, and fever.
- **Key feature:** Chest pain tends to worsen in the supine position and with inspiration. Classic patient seen sitting up and bending forward.

MNEMONIC

Causes of pericarditis—

CARDIAC RIND

Collagen vascular disease
Aortic dissection
Radiation
Drugs
Infections
Acute renal failure
Cardiac (MI)

Rheumatic fever
Injury
Neoplasms
Dressler syndrome

TABLE 2.1-16. Major Classes of Antihypertensive Agents

Class	Agents	Mechanism of Action	Side Effects
Diuretics	Thiazide, loop, K^+ sparing	↓ extracellular fluid volume and thereby ↓ vascular resistance.	Hypokalemia (not with K^+ sparing), hyperglycemia, hyperlipidemia, hyperuricemia, azotemia.
β-blockers	Propranolol, metoprolol, nadolol, atenolol, timolol, carvedilol, labetalol	↓ cardiac contractility and renin release.	Bronchospasm (in severe active asthma), bradycardia, CHF exacerbation, impotence, fatigue, depression.
ACEIs	Captopril, enalapril, fosinopril, benazepril, lisinopril	Block aldosterone formation, reducing peripheral resistance and salt/water retention.	Cough, angioedema, rashes, leukopenia, hyperkalemia.
ARBs	Losartan, valsartan, irbesartan	Block aldosterone effects, reducing peripheral resistance and salt/water retention.	Rashes, leukopenia, and hyperkalemia but no cough.
CCBs	Dihydropyridines (nifedipine, felodipine, amlodipine), nondihydropyridines (diltiazem, verapamil)	↓ smooth muscle tone and cause vasodilation; may also ↓ cardiac output.	**Dihydropyridines:** Headache, flushing, peripheral edema. **Nondihydropyridines:** ↓ contractility.
Vasodilators	Hydralazine, minoxidil	↓ peripheral resistance by dilating arteries/arterioles.	**Hydralazine:** Headache, lupus-like syndrome. **Minoxidil:** Orthostasis, hirsutism.
α_1-adrenergic blockers	Prazosin, terazosin, phenoxybenzamine	Cause vasodilation by blocking actions of norepinephrine on vascular smooth muscle.	Orthostatic hypotension.
Centrally acting adrenergic agonists	Methyldopa, clonidine	Inhibit the sympathetic nervous system via central α_2-adrenergic receptors.	Somnolence, orthostatic hypotension, impotence, rebound HTN.

- **Examination:** May reveal a pericardial friction rub. Elevated JVP and pulsus paradoxus (a ↓ in systolic BP > 10 mm Hg on inspiration) can be present with tamponade.

KEY FACT

ST-segment elevations in pericarditis are differentiated from MI in that they are not localized to 1 region of the heart.

Diagnosis

- **Initial tests:** CXR, ECG, and echocardiogram to rule out MI and pneumonia.
- **ECG changes:** Include **diffuse ST-segment elevation and PR-segment depressions** followed by T-wave inversions (see Figure 2.1-14).
- Pericardial thickening or effusion may be evident on echocardiography.

Treatment

- Address the underlying cause (eg, corticosteroids/immunosuppressants for SLE, dialysis for uremia) or symptoms (eg, ASA for post-MI pericarditis,

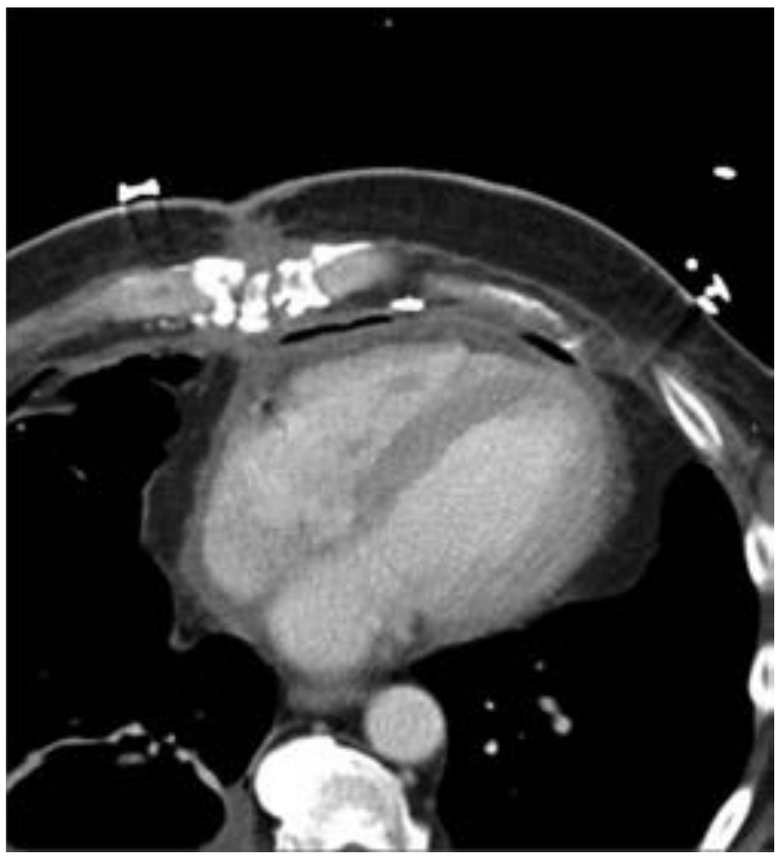


FIGURE 2.1-13. Radiographic findings in pericarditis Contrast enhanced CT at the level of the interventricular septum demonstrates a small pericardial effusion, with thickening and increased enhancement of the pericardium consistent with infection in this post-surgical patient. The air outlining the pericardium anteriorly is the result of dehiscence of the median sternotomy. (Reproduced with permission from USMLE-Rx.com.)

ASA/NSAIDs for viral pericarditis). Avoid corticosteroids within a few days after MI, as they can predispose to ventricular wall rupture.

- Pericardial effusions without symptoms can be monitored, but evidence of tamponade requires pericardiocentesis with continuous drainage as needed.

CARDIAC TAMPONADE

Excess fluid in the pericardial sac, leading to compromised ventricular filling and ↓ cardiac output. The rate of fluid formation is more important than the size of the effusion. Risk factors include pericarditis, malignancy, SLE, TB, and trauma (commonly stab wounds medial to the left nipple).

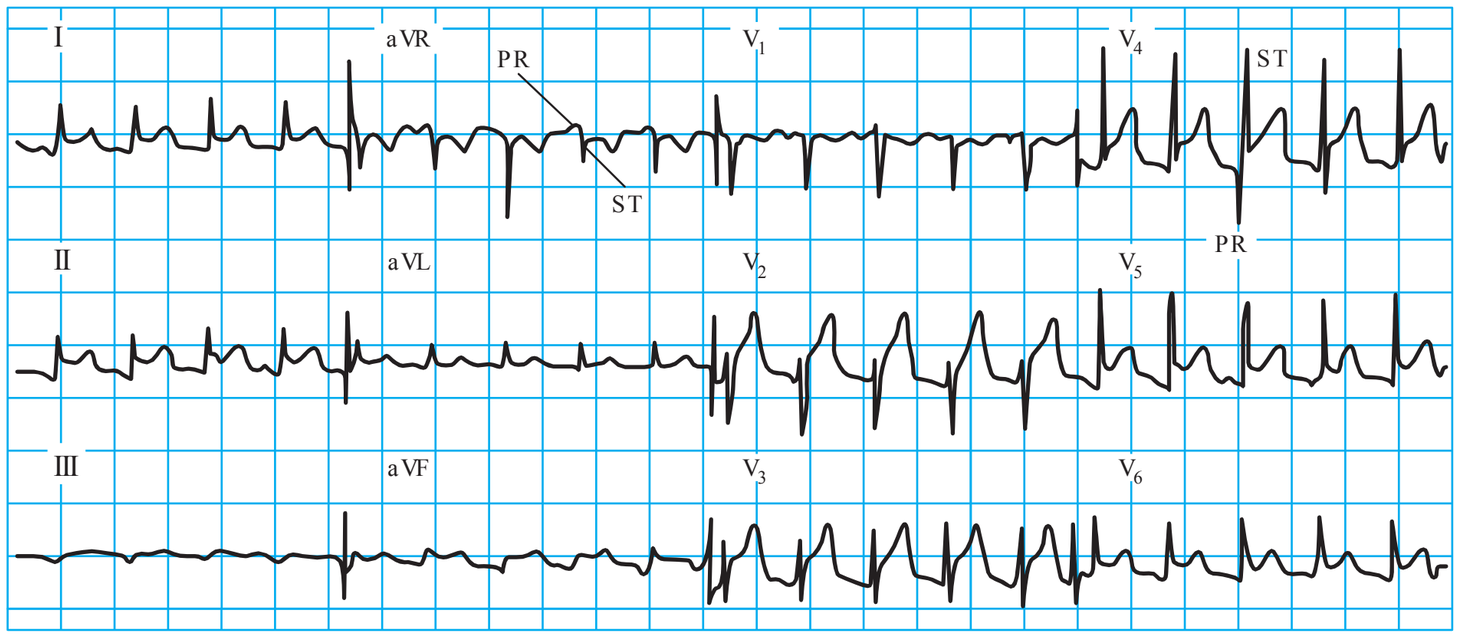


FIGURE 2.1-14. Acute pericarditis. Diffuse ST-segment elevations in multiple leads not consistent with any discrete coronary vascular territory and PR-segment depressions. (Reproduced with permission from Fauci AS et al. Harrison's Principles of Internal Medicine, 17th ed. New York, NY: McGraw-Hill; 2008.)

Q

A 20-year-old man presents with an initial BP of 150/85 mm Hg, and repeat measurement yields 147/85 mm Hg. The patient's potassium level is 3.2 mg/dL. What is the next appropriate diagnostic step?

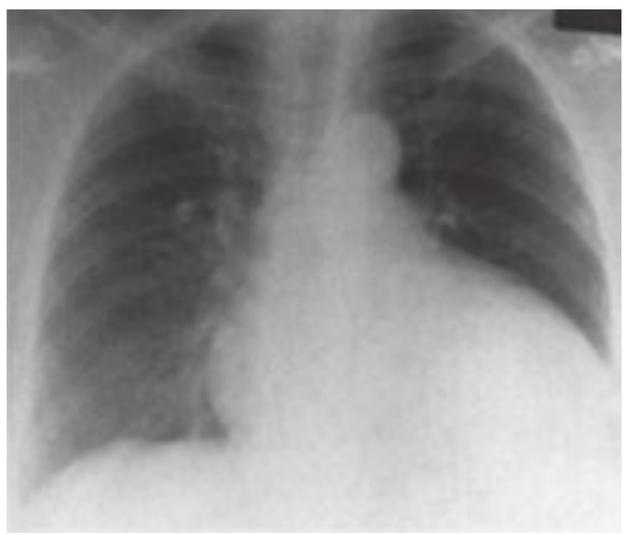


FIGURE 2.1-15. Water-bottle-shaped heart seen on chest x-ray film with pericardial effusion. (Reproduced with permission from Chen MY et al. Basic Radiology, 2nd ed. New York, NY: McGraw-Hill; 2011.)

KEY FACT

Beck triad can diagnose acute cardiac tamponade:
- JVD
- Hypotension
- Distant heart sounds

History/Pe

- Presents with fatigue, dyspnea, anxiety, tachycardia, and tachypnea that can rapidly progress to shock and death.
- Examination of a patient with acute tamponade may reveal Beck triad (hypotension, distant heart sounds, and JVD), a narrow pulse pressure, pulsus paradoxus, and Kussmaul sign (increased JVD on inspiration).

Diagnosis

- **Echocardiogram** shows right atrial and right ventricular diastolic collapse.
- **CXR** may show an enlarged, globular, water-bottle-shaped heart with a large effusion (see Figure 2.1-15).
- If present on ECG, **electrical alternans is diagnostic** of a large pericardial effusion.

Treatment

- Aggressive volume expansion with IV fluids.
- Urgent pericardiocentesis (aspirate will be nonclotting blood).
- Decompensation may warrant pericardial window.

Valvular Heart Disease

Until recently, rheumatic fever (which affects the mitral valve more often than the aortic valve) was the most common cause of valvular heart disease in US adults; the leading cause is now mechanical degeneration. Subtypes are listed in Table 2.1-17 along with their etiologies, presentation, diagnosis, and treatment.

Vascular Disease

AORTIC ANEURYSM

Greater than 50% dilatation of all three layers of the aortic wall. Aortic aneurysms are most commonly **associated with atherosclerosis.** Most are abdominal and > 90% originate below the renal arteries.

KEY FACT

Size of AAA determines treatment:
- < 5 cm → monitoring
- > 5 cm → surgical repair

A

A hyperaldosteronism workup with serum aldosterone and renin levels is an appropriate next diagnostic step.

History/Pe

- **Usually asymptomatic** and discovered incidentally on examination or radiologic study.
- Examination demonstrates a **pulsatile abdominal mass or abdominal bruits.**
- Risk factors include HTN, high cholesterol, other vascular disease, a ⊕ family history, smoking, gender (males > females), and age.
- Ruptured aneurysm leads to hypotension and severe, tearing abdominal pain that radiates to the back.

Diagnosis

- Screen all men 65–75 years of age with a history of smoking once by ultrasound for AAA (see Figure 2.1-16).
- Abdominal ultrasound is used for diagnosis or to follow an aneurysm over time.
- CT with contrast may be useful to determine the precise anatomy.

TABLE 2.1-17. Types of Valvular Heart Disease

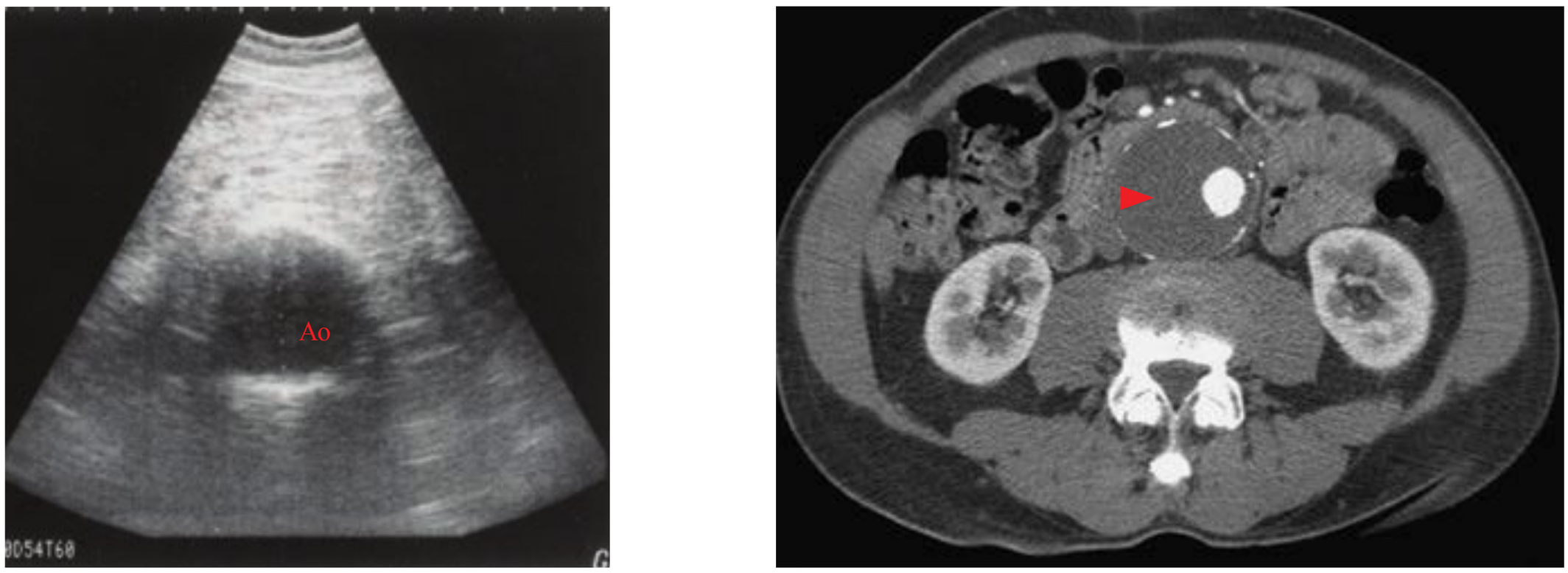
type	etiology	history	exam/diagnosis	treatment
Aortic stenosis	**Most often seen in the elderly.** Unicuspid and **bicuspid valves can lead to symptoms** in childhood and adolescence.	May be asymptomatic for years despite significa t stenosis. Once symptomatic, usually progresses from angina to syncope to CHF to death within 5 years. **Sx** (also indications for valve replacements): **ACS—Angina, CHF, Syncope.**	**PE: Pulsus parvus et tardus** (weak, delayed carotid upstroke) and a single or paradoxically split S2 sound; systolic murmur radiating to the carotids. **Dx:** Echocardiography.	Aortic valve replacement.
Aortic regurgitation	**Acute:** Infective endocarditis, aortic dissection, chest trauma. **Chronic:** Valve malformations, rheumatic fever, connective tissue disorders.	**Acute:** Rapid onset of pulmonary congestion, cardiogenic shock, and severe dyspnea. **Chronic:** Slowly progressive onset of dyspnea on exertion, orthopnea, and PND.	**PE: Blowing diastolic murmur** at the left sternal border, mid-diastolic rumble (Austin Flint murmur), and midsystolic apical murmur. **Widened pulse pressure** causes de Musset sign (head bob with heartbeat), Corrigan sign (water-hammer pulse), and Duroziez sign (femoral bruit). **Dx:** Echocardiography.	Vasodilator therapy (dihydropyridines or ACEIs) for isolated aortic regurgitation until symptoms become severe enough to warrant valve replacement.
Mitral valve stenosis	The most common etiology continues to be **rheumatic fever.**	Symptoms range from dyspnea, orthopnea, and PND to infective endocarditis and arrhythmias.	**PE:** Opening snap and **mid-diastolic murmur** at the apex; pulmonary edema. **Dx:** Echocardiography.	Antiarrhythmics (β-blockers, digoxin) for symptomatic relief; mitral balloon valvotomy and valve replacement are ef ective for severe cases.
Mitral valve regurgitation	Primarily 2° to **rheumatic fever or chordae tendineae rupture after MI.** Infective endocarditis.	Patients present with dyspnea, orthopnea, and fatigue.	**PE: Holosystolic murmur** radiating to the axilla. **Dx:** Echocardiography will demonstrate regurgitant fl w; angiography can assess the severity of disease.	Antiarrhythmics if necessary (AF is common with LAE; nitrates and diuretics to ↓ preload). Valve repair or replacement for severe cases.

Treatment

- In asymptomatic patients, monitoring is appropriate for lesions < 5 cm.
- Surgical repair is indicated if the lesion is > 5.5 cm (abdominal), > 6 cm (thoracic), or smaller but rapidly enlarging.
- Emergent surgery for symptomatic or ruptured aneurysms.

Q

A 70-year-old man with HTN presents for a routine appointment. He quit smoking 20 years ago but has a 20-pack-year history. What screening, if any, is indicated?



A B

FIGURE 2.1-16. Abdominal aortic aneurysm. (A) Ultrasound image of an AAA (Ao = aorta). **(B)** Transaxial image from a contrast-enhanced CT showing an aneurysm with extensive mural thrombus (arrowhead). (Image A reproduced with permission from Tintinalli JE et al. Tintinalli's Emergency Medicine: A Comprehensive Study Guide, 6th ed. New York, NY: McGraw-Hill; 2004. Image B reproduced with permission from Doherty GM. Current Diagnosis & Treatment: Surgery, 13th ed. New York, NY: McGraw-Hill; 2010.)

KEY FACT

Aortic aneurysm is most often associated with atherosclerosis, whereas aortic dissection is commonly linked to HTN.

AORTIC DISSECTION

A transverse tear in the intima of a vessel that results in blood entering the media, creating a false lumen and leading to a hematoma that propagates longitudinally. **Most commonly 2° to HTN.** The most common sites of origin are above the aortic valve and distal to the left subclavian artery. Most often occurs at 40–60 years of age, with a greater frequency in males than in females.

History/Pe

- **Presentation: Sudden tearing/ripping pain in the anterior chest** (ascending) or back (descending).
- **Examination:**
  - Patients are typically hypertensive. If hypotensive, consider pericardial tamponade, hypovolemia from blood loss, or other cardiopulmonary etiologies.
  - **Asymmetric pulses and BP measurements.**
  - A murmur of aortic regurgitation may be heard if the aortic valve is involved with a proximal dissection.
  - **Neurologic deficits** may be seen if the **aortic arch or spinal arteries** are involved.
- Signs of pericarditis or pericardial tamponade may be seen.

KEY FACT

Ascending aortic dissections are surgical emergencies; descending dissections are still emergencies but can often be treated medically.

Diagnosis

- **CT angiography** is the gold standard of imaging. MRA can be used if contrast CT is contraindicated. TEE may also be used to visualize details of the proximal aorta and coronary vessels and can also evaluate for pericardial effusion.
- The **Stanford system** classifies any dissection proximal to the left subclavian artery as type A and all others as type B (see Figure 2.1-17).

A

The United States Preventive Services Task Force (USPSTF) guidelines recommend one-time screening for AAA by ultrasound in men ages 65–75 who have ever smoked.

Treatment

- Monitor and medically manage BP and heart rate as necessary. Avoid thrombolytics. Begin β-blockade before starting vasodilators to prevent reflex tachycardia.

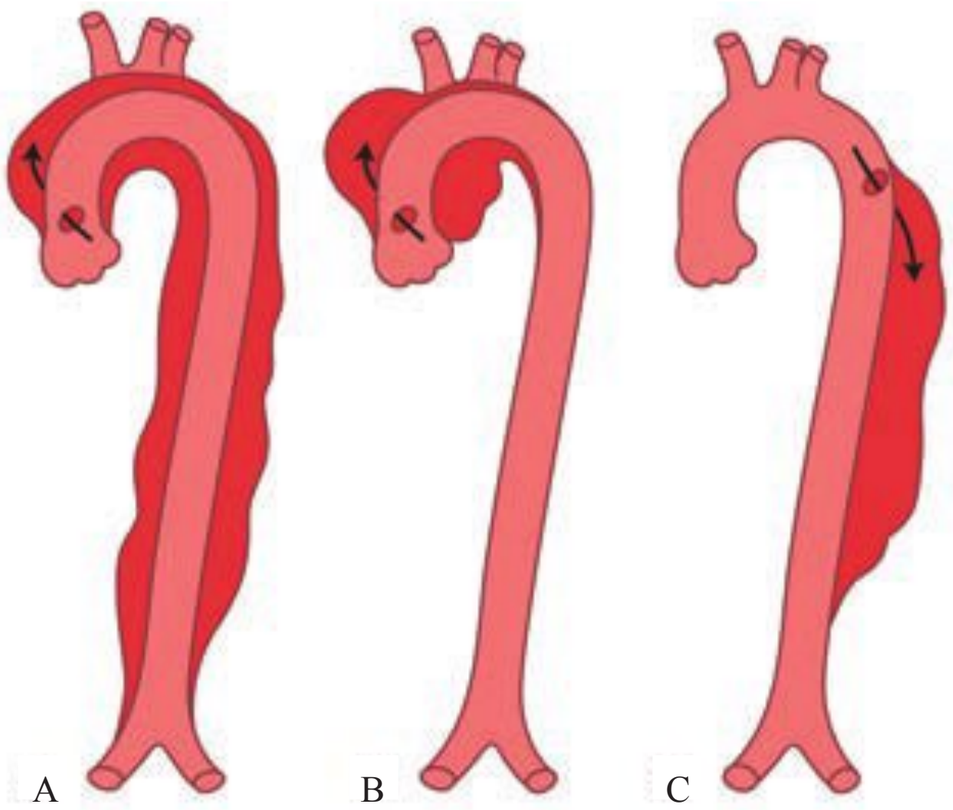


FIGURE 2.1-17. Aortic dissection. Stanford classification of aortic dissections. Shown are **(A, B)** proximal or ascending types and **(C)** descending type. (Reproduced with permission from USMLE-Rx.com.)

- If the dissection involves the ascending aorta, it is a surgical emergency; descending dissections can often be managed with BP and heart rate control.

DEEP VENOUS THROMBOSIS

Clot formation in the large veins of the extremities or pelvis. The classic **Virchow triad** of risk factors includes venous stasis (eg, from plane flights, bed rest, or incompetent venous valves in the lower extremities), endothelial trauma (eg, surgery, injury to the lower extremities), and hypercoagulable states (eg, malignancy, pregnancy, OCP use).

History/Pe

- Presents with unilateral lower extremity pain and swelling.
- **Homans sign** is calf tenderness with passive foot dorsiflexion (poor sensitivity and specificity for DVT).

Diagnosis

Doppler ultrasound; a spiral CT or V/Q scan may be used to evaluate for PE (see Figure 2.1-18).

Treatment

- Anticoagulate with IV unfractionated heparin or subcutaneous low-molecular-weight heparin (LMWH) followed by PO warfarin for a total of 3–6 months.
- In patients with contraindications for anticoagulation, inferior vena cava filters should be placed.
- Hospitalized patients should receive DVT prophylaxis consisting of exercise as tolerated, antithromboembolic stockings, and subcutaneous unfractionated heparin or LMWH.

KEY FACT

Virchow triad: (1) hemostasis, (2) trauma (endothelial damage), (3) hypercoagulability.

KEY FACT

A ⊖ D-dimer test can be used to rule out the possibility of PE in low-risk patients.

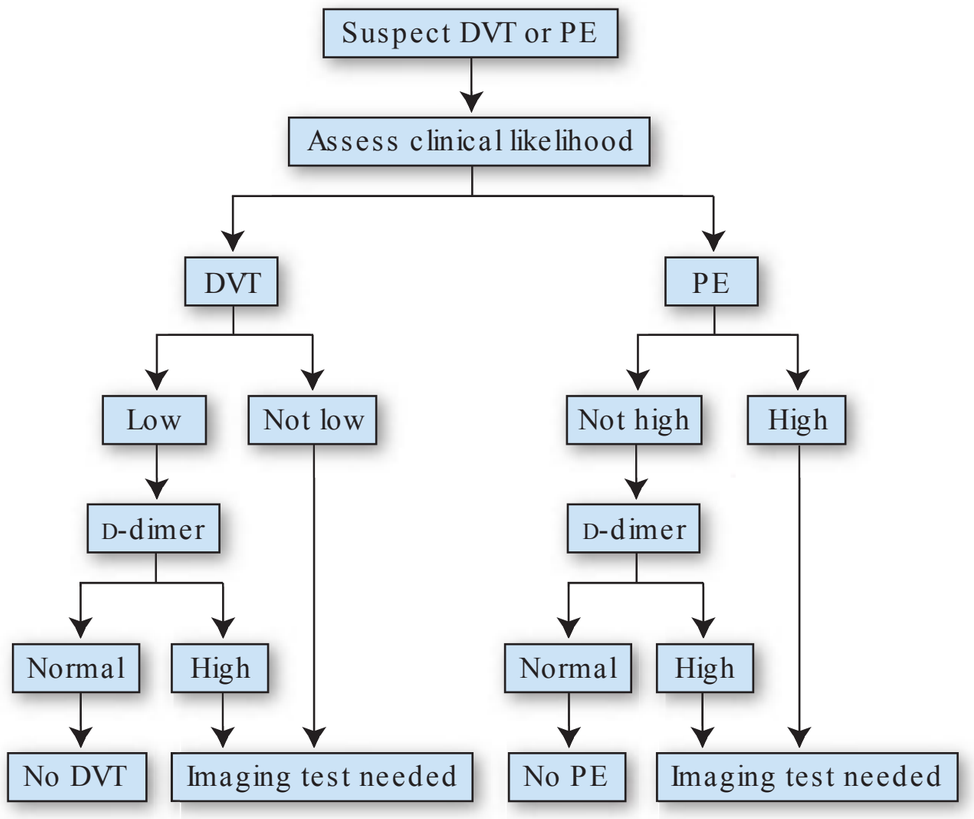


FIGURE 2.1-18. Algorithm for diagnostic imaging of deep-vein thrombosis and pulmonary embolism. (Reproduced with permission from Fauci AS et al. Harrison's Principles of Internal Medicine, 17th ed. New York, NY: McGraw-Hill; 2008.)

PERIPHERAL ARTERIAL DISEASE

Defined as a restriction of the blood supply to the extremities by atherosclerotic plaque. The lower extremities are most commonly affected. Clinical manifestations depend on the vessels involved, the extent and rate of obstruction, and the presence of collateral blood flow.

History/PE

- Presents with intermittent claudication (reproducible leg pain that occurs with walking and is relieved with rest). As the disease progresses, pain occurs at rest and affects the distal extremities. Dorsal foot ulcerations may develop 2° to poor perfusion. A painful, cold, numb foot is characteristic of critical limb ischemia.
- For more proximal lesions, there will be claudication and weak pulses below the area of occlusion (ie, aortoiliac disease will produce buttock claudication and decreased femoral pulses).
- **Acute ischemia:**
  - Most often caused by embolization from the heart; acute occlusions commonly occur at bifurcations distal to the last palpable pulse (see mnemonic).
  - May also be 2° to cholesterol atheroembolism ("blue toe syndrome").
- **Chronic ischemia:** Lack of blood perfusion leads to muscle atrophy, pallor, cyanosis, hair loss, and gangrene/necrosis.

MNEMONIC

The 6 P's of acute ischemia:

Pain
Pallor
Paralysis
Pulse defici
Paresthesias
Poikilothermia

Diagnosis

- Measurement of ankle and brachial systolic BP (ankle-brachial index, or ABI) can provide objective evidence of atherosclerosis (rest pain usually occurs with an ABI < 0.4). A very high ABI can indicate calcification of the arteries.
- Doppler ultrasound helps identify stenosis and occlusion. Normal ankle Doppler readings are > 90% of brachial readings.
- Arteriography and digital subtraction angiography are necessary for surgical evaluation.

Treatment

- Control underlying conditions (DM, tobacco), and institute careful hygiene and foot care. **Exercise helps develop collateral circulation.**
- ASA, cilostazol, and thromboxane inhibitors may improve symptoms.
- Angioplasty and stenting have a variable success rate that is dependent on the area of occlusion.
- Surgery (arterial bypass) or amputation can be employed when conservative treatment fails.

KEY FACT

$ABI = P_{leg} / P_{arm}$
ABI < 0.4 with rest pain (normal ABI: 1.0–1.2)

LYMPHEDEMA

A disruption of the lymphatic circulation that results in peripheral edema and chronic infection of the extremities. Primary (or congenital) lymphedema is rare. Most often caused secondarily by surgeries involving lymph node dissection or, in developing countries, parasitic infections.

History/Pe

History will differ by cause. Examples include:

- Postmastectomy patients present with unexplained swelling of the upper extremity (secondary to surgery).
- Immigrants present with progressive swelling of the lower extremities bilaterally with no cardiac abnormalities (ie, filariasis infection).
- Children present with progressive, bilateral swelling of the extremities (1°).
- Patients with Turner syndrome will have lymphatic edema.

Diagnosis

Diagnosis is clinical. Rule out other causes of edema, such as cardiac and metabolic disorders.

Treatment

- Directed at symptom management, including exercise, massage therapy, and pressure garments to mobilize and limit fluid accumulation.
- Diuretics are ineffective and relatively contraindicated.
- Maintain vigilance for cellulitis with prompt gram-⊕ antibiotic coverage for infection.

Syncope

A sudden, temporary loss of consciousness and postural tone 2° to cerebral hypoperfusion. Etiologies can be cardiac, neurologic, or other.

- **Cardiac:** Valvular lesions, arrhythmias, PE, cardiac tamponade, aortic dissection.
- **Neurologic:** Subarachnoid hemorrhage.
- **Other:** Orthostatic/hypovolemic hypotension, metabolic abnormalities, neurocardiogenic syndromes (eg, vasovagal/micturition syncope), psychiatric, medications.

History/Pe

- Age, triggers, prodromal symptoms, and associated symptoms should be investigated.
- Syncope can be confused with seizures. Unlike syncope, seizures may be characterized by a preceding aura, tonic-clonic activity, tongue-biting, bladder and bowel incontinence, and a postictal phase.

KEY FACT

Cardiac syncope is associated with 1-year sudden cardiac death rates of up to 40%.

- Cardiac causes of syncope are typically associated with very brief or absent prodromal symptoms, a history of exertion, lack of association with changes in position, and/or a history of cardiac disease.
- Neurocardiogenic syndrome is common in younger patients.

Diagnosis

Depending on the suspected etiology:

- **Cardiac:** ECG, Holter monitors or event recorders (arrhythmias), echocardiograms (structural abnormalities), stress tests (ischemia).
- **Neurologic:** CT of head (ischemia or hemorrhage) and EEG (seizure).
- **Other:** Orthostatic BP readings (hypovolemia, autonomic dysfunction), glucose (hypoglycemia), and tilt-table testing (neurally mediated syncope).

Treatment

Tailored to the etiology.

HIGH-YIELD FACTS IN

DERMATOLOGY

Layers of the Skin 50

Allergic and Immune-Mediated Skin Disorders 50
- Hypersensitivity Reactions 50
- Atopic dermatitis (Eczema) 50
- contact dermatitis 51
- Seborrheic dermatitis 54
- Stasis dermatitis 55
- Psoriasis 56
- Urticaria (Hives) 57
- drug Eruption 57
- Erythema Multiforme 58
- Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis 59
- Erythema Nodosum 60
- Bullous Pemphigoid/Pemphigus Vulgaris 60

Infectious Disease Manifestations of the Skin 62
- Viral diseases 62
- Bacterial Infections 65
- Fungal Infections 69
- Parasitic Infections 72

Ischemic Disorders of the Skin 73
- decubitus Ulcers 73
- Gangrene 73

Miscellaneous Skin Disorders 74
- Acanthosis Nigricans 74
- Lichen Planus 75
- Rosacea 75
- Pityriasis Rosea 76
- Vitiligo 76
- Eyelid Lesions 77

Neoplasms of the Skin 77
- Seborrheic Keratosis 77
- Actinic Keratosis 77
- cutaneous Squamous cell carcinoma 78
- Basal cell carcinoma 78
- Melanoma 79
- Kaposi Sarcoma 80
- Mycosis Fungoides (cutaneous T-cell Lymphoma) 81
- cherry Angiomas (Hemangiomas) 81

Layers of the Skin

Figures 2.2-1 and 2.2-2 and Table 2.2-1 outline the skin layers, cell junctions, and common terminology.

Allergic and Immune-Mediated Skin Disorders

HYPERSENSITIVITY REACTIONS

Table 2.2-2 outlines the types and mechanisms of hypersensitivity reactions.

ATOPIC DERMATITIS (ECZEMA)

A chronic inflammatory skin disorder that often starts in infancy and persists into adulthood. It is characterized by **pruritus leading to lichenification** (see Figure 2.2-3).

KEY FACT

Long-term use of immunomodulator medications ↑ the risk of developing **lymphoma.**

HISTORY/PE

- Look for a strong **family history** of **asthma, eczema, and allergic rhinitis** ("atopic triad").
- Patients are at ↑ risk of 2° bacterial (Staphylococcus aureus) and viral (HSV or molluscum) infection due to constant waxing and waning cycles of pruritus and **scratching.**
- Triggers include climate, food, skin irritants, allergens, and emotional factors.
- Manifestations by age group:
  - **Infants:** Erythematous, edematous, weeping, pruritic papules and plaques on the face, scalp, and extensor surfaces of the extremities. **The diaper area is often spared.**
  - **Children:** Dry, scaly, pruritic, excoriated papules, plaques in the **flexural** areas and neck.
  - **Adults:** Lichenification and dry, fissured skin in a flexural distribution. Often, there is hand or eyelid involvement.

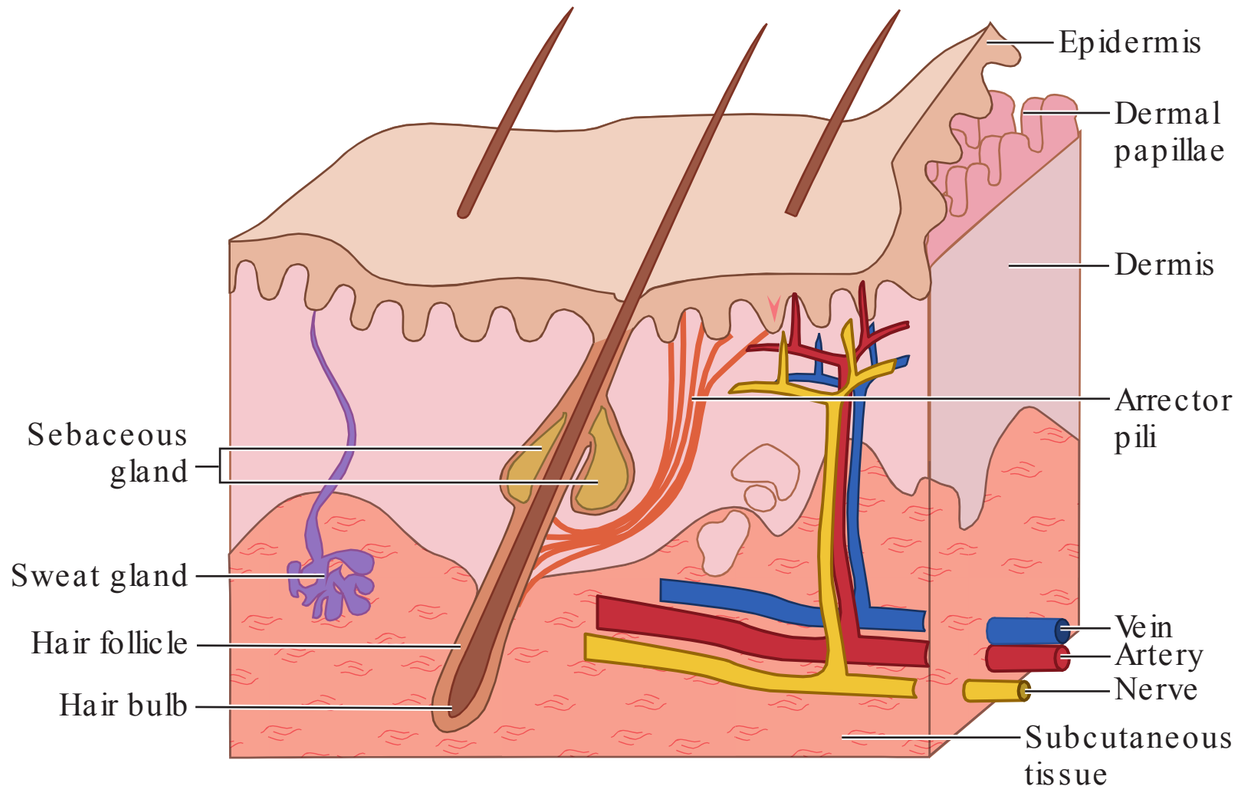


FIGURE 2.2-1. Layers of the skin. (Adapted with permission from Hardman JG et al. Goodman and Gilman's The Pharmacological Basis of Therapeutics, 10th ed. New York, NY: McGraw-Hill; 2001.)

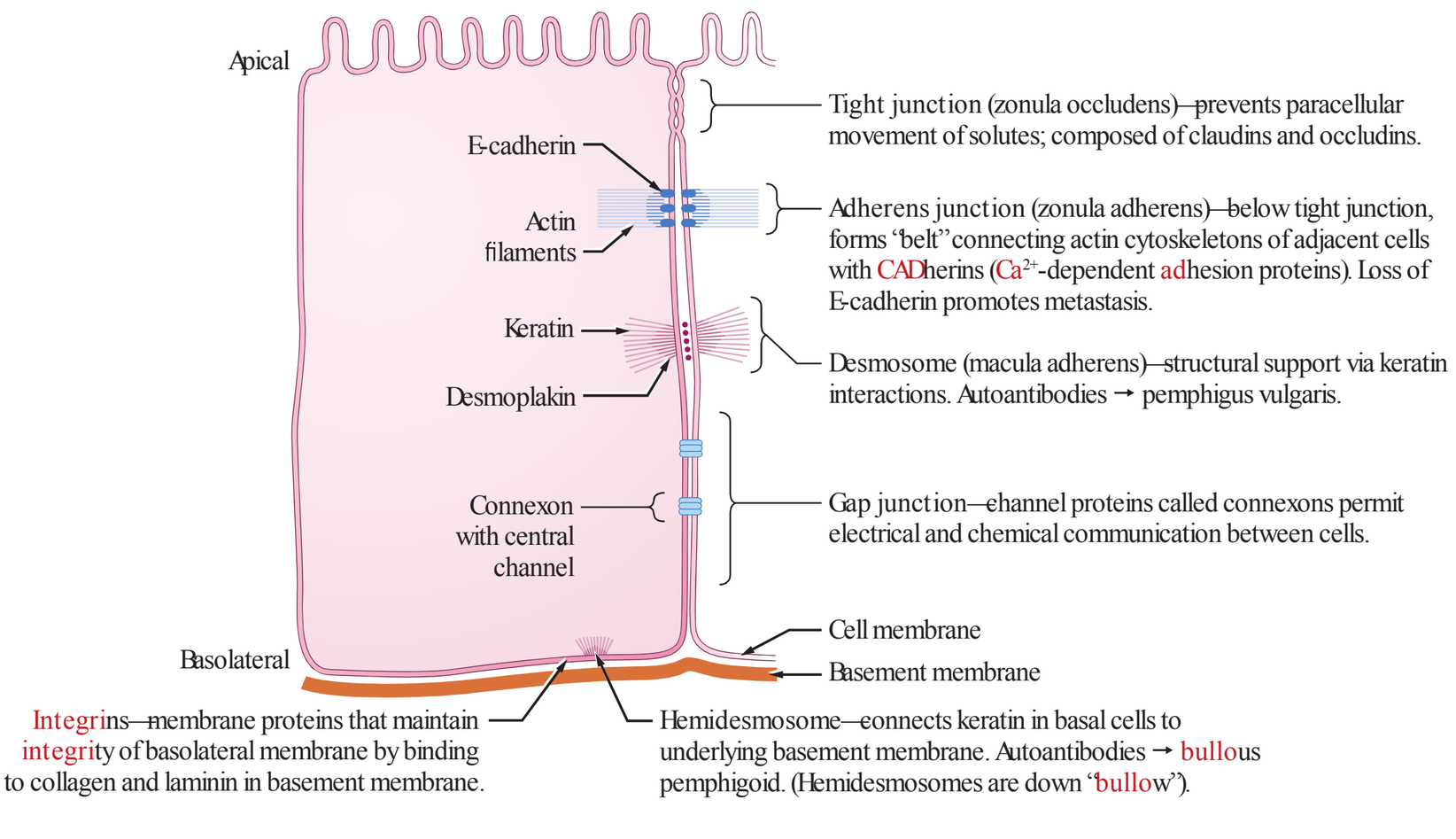


FIGURE 2.2-2. Epithelial cell junctions. (Reproduced with permission from USMLE-Rx.com.)

Diagnosis

Clinical. KOH prep can help distinguish eczema from a tinea infection. Mild eosinophilia and ↑ IgE may be seen in some patients, but these are not used to make the diagnosis.

Treatment

- **Topical corticosteroids are first-line therapy.** Topical immunomodulators (eg, tacrolimus) are useful as steroid sparing agents for moderate to severe eczema for patients > 2 years of age.
- Topical steroids should be used intermittently to avoid skin atrophy.
- **Skin care:** Goal is to break the itching and scratching cycle. Use gentle soaps and moisturize after bathing, avoid irritants, and use antihistamines to control pruritus.

KEY FACT

Erythema toxicum neonatorum typically begins 1–3 days after delivery and resembles eczema, presenting with red papules, pustules, and/or vesicles with surrounding erythematous halos. ↑ eosinophils are present in the pustules or vesicles. This benign eruption usually resolves in 1–2 weeks with no treatment.

CONTACT DERMATITIS

A type IV hypersensitivity reaction that results from contact with an allergen to which the patient has previously been exposed and sensitized such as **nickel, poison ivy, perfumes/deodorants and neomycin.** More common in adults.

History/Pe

- Presents with pruritus and rash, with the shape of the rash often mimicking the exposing object (see Figure 2.2-4). Characteristic distributions are seen where makeup, clothing, perfume, **nickel jewelry,** and plants come into contact with the skin.
- Often described as a "linear" or "angular" rash. It can spread over the body via transfer of allergen by the hands or via circulating T lymphocytes.
- Frequently implicated allergens: **Poison ivy,** poison oak, **nickel, topical antibiotics,** cosmetics. Latex allergy is not a contact dermatitis—it is a type I hypersensitivity reaction.

TABLE 2.2-1. Dermatologic Macroscopic Terms

Lesion	Characteristics	Examples
Macule	Flat lesion with well-circumscribed change in skin color < 1 cm	Freckle, labial macule (Figure A)
Patch	Macule > 1 cm	Birthmark (congenital nevus) (Figure B)
Papule	Elevated solid skin lesion < 1 cm	Mole (nevus) (Figure C), acne
Plaque	Papule > 1 cm	Psoriasis (Figure D)
Vesicle	Small fluid containing blister < 1 cm	Chickenpox (varicella), shingles (zoster) (Figure E)
Bulla	Large fluid containing blister > 1 cm	Bullous pemphigoid (Figure F)
Cyst	Epithelium-lined sac containing flui	Pilar cyst (epidermal cyst on scalp)
Pustule	Vesicle containing pus	Pustular psoriasis (Figure G)
Wheal	Transient smooth papule or plaque	Hives (urticarial) (Figure H)
Scale	Flaking off of st atum corneum	Eczema, psoriasis, SCC (Figure I)
Crust	Exudate of dried serum, blood, pus	Impetigo (Figure J)
Ulcer	A deep depression resulting from destruction of the epidermis and upper dermis	Diabetic foot ulcer
Lichenific tion	Hypertrophy and thickening of the epidermis with accentuation of normal skin markings	Chronic scratching (pruritic scabies, eczema)



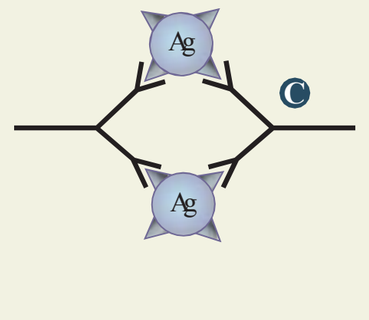
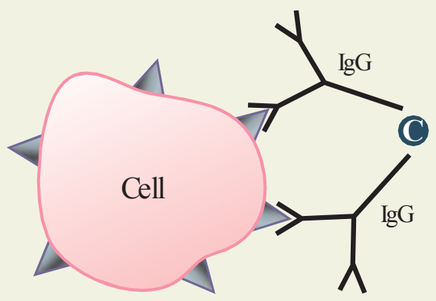
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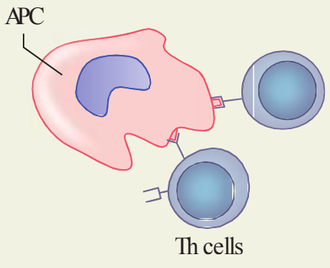
Used with permission from Dr. Richard Usatine.

TABLE 2.2-2. Types and Mechanisms of Hypersensitivity Reactions

Description	Mechanism	Comments	Examples
		Type I	
Anaphylactic and atopic  	Antigen cross-links **IgE** on presensitized mast cells and basophils, triggering the release of vasoactive amines like **histamine.** Reaction develops rapidly as a result of preformed antibody.	**F**irst and **F**ast (like anaphylaxis). Types I, II, and III are all antibody mediated.	Anaphylaxis (bee sting, food allergy), asthma, urticaria, urticarial drug reactions, local wheal and flare.
		Type II	
Cytotoxic  C = complement	**IgM** and **IgG** bind to antigen on an "enemy" cell, leading to lysis by complement or phagocytosis.	Cy-**2**-toxic. Antibody and complement lead to MAC.	Autoimmune hemolytic anemia, erythroblastosis fetalis, Goodpasture syndrome, rheumatic fever.
		Type III	
Immune complex 	Antigen-antibody complexes activate complement, which attracts PMNs; PMNs release lysosomal enzymes.	Imagine an immune complex as 3 things stuck together: antigen-antibody-complement. Includes many glomerulonephritides and vasculitides.	Polyarteritis nodosa, immune complex glomerulonephritis, SLE, rheumatoid arthritis.
Serum sickness	Antibodies to the foreign proteins are produced in □5 days. Immune complexes form and are deposited in membranes, where they lead to tissue damage by fixing complement.	Most serum sickness is now caused by drugs (not serum). Fever, urticaria, arthralgias, proteinuria, and lymphadenopathy occur 5–10 days after antigen exposure. More common than Arthus reaction.	Drug reaction.
Arthus reaction	A local reaction to antigen by **preformed antibodies** characterized by vascular necrosis and thrombosis.	Arthus reaction occurs rarely 4–12 hours after vaccination.	Hypersensitivity pneumonitis.

(continues)

TABLE 2.2-2. Types and Mechanisms of Hypersensitivity Reactions (continued)

Description	Mechanism	Comments	Examples
		Type IV	
Delayed (cell-mediated) type 	**Sensitized T lymphocytes** encounter Ag and then release lymphokines (leading to macrophage activation).	**4th** and last—**delayed. Cell mediated,** not antibody mediated; therefore, it is not transferable by serum.	TB skin tests, transplant rejection, contact dermatitis.

Reproduced with permission from Le T et al. First Aid for the USMLE Step 1 2015. New York, NY: McGraw-Hill; 2015.

Diagnosis

Clinical. **Patch testing** can be used to establish the causative allergen after the acute-phase eruption has been treated.

Treatment

First-line treatment is **topical corticosteroids and allergen avoidance.** In severe cases a systemic corticosteroid may be needed.

SEBORRHEIC DERMATITIS

A common **chronic inflammatory skin disease** that may be caused by a hypersensitivity reaction to Malassezia furfur, a generally harmless yeast found in **sebum and hair follicles.** It has a predilection for **areas with sebaceous glands.hbbc**



FIGURE 2.2-3. Atopic dermatitis. Lichenification, excoriations, and ill-defined, scaling erythema are characteristic. (Reproduced with permission from Tintinalli JE et al. Tintinalli's Emergency Medicine: A Comprehensive Study Guide, 7th ed. New York, NY: McGraw-Hill; 2011.)

History/Pe

- Rash presentation varies with age:
  - **Infants:** Severe, red diaper rash with yellow scale, erosions, and blisters. Scaling and crusting **("cradle cap")** may be seen on the scalp (see Figure 2.2-5A).
  - **Children/adults:** Red, scaly patches are seen around the ears, eyebrows, nasolabial fold, midchest, and scalp (see Figure 2.2-5B).
- Patients with **HIV/AIDS and Parkinson disease can develop severe seborrheic dermatitis.**

Diagnosis

Clinical. Can be confused with atopic dermatitis, contact dermatitis, or psoriasis.

Treatment

Treat adults with **selenium sulfide or zinc pyrithione shampoos** for the scalp, and topical antifungals (ketoconazole cream) and/or topical corticosteroids for other areas. Cradle cap often resolves with routine bathing and application of emollients in infants.

STASIS DERMATITIS

Lower extremity dermatitis due to **venous hypertension** forcing blood from the deep to the superficial venous system. Venous hypertension is often a result of venous valve incompetence or flow obstruction. Commonly involves the medial ankle in patients with DVT history, chronic edema, and long periods of standing. If untreated, the area can become inflamed, exudative, and hyperpigmented from hemosiderin deposition (see Figure 2.2-6). **Stasis ulcers may develop.** Treat early with **leg elevation, compression stockings,** emollients, and topical steroids.



A B

FIGURE 2.2-5. Seborrheic dermatitis. (A) Seborrheic dermatitis (cradle cap) in an infant. Note the yellow, scaly crust present on the infant's scalp with an area of erosion. **(B)** Photo-exacerbated seborrheic dermatitis, affecting the face only at sites of predilection for the seborrheic eruption. (Part A reproduced with permission from Tintinalli JE et al. Tintinalli's Emergency Medicine: A Comprehensive Study Guide, 7th ed. New York, NY: McGraw-Hill; 2011. Part B reproduced with permission from Goldsmith LA et al. Fitzpatrick's Dermatology in General Medicine, 8th ed. New York, NY: McGraw-Hill; 2012.)



FIGURE 2.2-4. Contact dermatitis. Shown are erythematous papules and vesicles with serous weeping localized to areas of contact with the offending agent. (Reproduced with permission from Hurwitz RM. Pathology of the Skin: Atlas of Clinical-Pathological Correlation, 2nd ed. Stamford, CT: Appleton & Lange; 1998.)



FIGURE 2.2-6. Stasis dermatitis. Venous ulceration with stasis dermatitis, edema, and varicosities. (Reproduced with permission from Goldsmith LA et al. Fitzpatrick's Dermatology in General Medicine, 8th ed. New York, NY: McGraw-Hill; 2012.)

Q

An infant with a history of eczema treated with corticosteroids is brought in with a new-onset rash and fever. Physical examination reveals grouped vesicles involving eczematous areas of the infant's extremities and face. What is the appropriate therapy?

PSORIASIS

A T-cell-mediated inflammatory dermatosis characterized by **erythematous plaques with silvery scales** (see Figure 2.2-7A) due to dermal inflammation and epidermal hyperplasia. Psoriasis can begin at any age.

History/Pe

- Lesions are classically found on the **extensor surfaces,** including the elbows and knees. Scalp and lumbosacral regions are often involved. Nails are frequently affected with pitting, "oil spots," and onycholysis (lifting of the nail plate, see Figure 2.2-7B).
- Lesions initially appear small but may become confluent and can be provoked by local irritation or trauma **(Koebner phenomenon).** Some medications such as β-blockers, lithium, ACEIs, can worsen psoriatic lesions.
- Up to 30% develop **psoriatic arthritis** (affecting small joints of hands and feet).

KEY FACT

A rash involving the extensor surfaces? Think psoriasis. A rash involving the flexor surfaces? Think atopic dermatitis.

Diagnosis

- Clinical. "Classical" presentation: **Auspitz sign (pinpoint bleeding when scale is scraped).**
- Biopsy if diagnosis is uncertain. Histology shows a thickened epidermis, elongated rete ridges, an absent granular cell layer, preservation of nuclei in the stratum corneum (parakeratosis), and a sterile neutrophilic infiltrate in the stratum corneum **(Munro microabscess).**

KEY FACT

Prior to starting methotrexate or anti-TNF biologics, patients should at a minimum get a CBC, CMP, hepatitis panel, and a PPD.

Treatment

- Local disease: Manage with **topical steroids,** calcipotriene (vitamin D derivative) and tazarotene (vitamin A derivative).
- Severe disease or presence of psoriatic arthritis: **Methotrexate or anti-TNF biologics** (etanercept, infliximab, adalimumab). UV light therapy can be used for extensive skin involvement (except in immunosuppressed patients who can develop skin cancer from UV).

KEY FACT

"Sausage digits" and pencil-in-cup x-ray deformities are found in psoriatic arthritis.



A B

FIGURE 2.2-7. Psoriasis. (A) Skin changes. The classic sharply demarcated plaques with silvery scales are commonly located on the extensor surfaces (eg, elbows, knees). **(B) Nail changes.** Note the pitting, onycholysis, and "oil spots." (Part A reproduced with permission from Wolff K et al. Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology, 7th ed. New York, NY: McGraw-Hill; 2013. Part B reproduced with permission from Hurwitz RM. Pathology of the Skin: Atlas of Clinical-Pathological Correlation, 2nd ed. Stamford, CT: Appleton & Lange; 1998.)

A

This infant has eczema herpeticum, a medical emergency that is due to the propensity for HSV infection to spread systemically, potentially affecting the brain. IV acyclovir must be started immediately!

URTICARIA (HIVES)

Results from the release of **histamine and prostaglandins from mast cells in a type I hypersensitivity response.** It is characterized by superficial, intense erythema and edema in a localized area. Can be acute or chronic (lasting > 6 weeks).

History/Pe

- Urticaria lesions (wheals) are reddish or white transient papules or plaques representing dermal edema. Lesions are widespread and last a few hours.
- Lesions may become confluent and form circular or sinusoidal patterns.
- In severe allergic reactions, **extracutaneous manifestations** can include tongue swelling, angioedema (deep, diffuse swelling often around the eyes and mouth; see Figure 2.2-8), asthma, GI symptoms, joint swelling, and fever.
- Acute urticaria is a response to some often unidentified trigger: food, drug, virus, insect bite, or physical stimulus (cold, heat, sun). Chronic urticaria is usually idiopathic.

Diagnosis

Clinical impression. It can often be difficult to determine the cause.

Treatment

Treat urticaria with **systemic antihistamines.** Anaphylaxis (rare) requires epinephrine IM, antihistamines, IV fluids, and airway maintenance.

DRUG ERUPTION

Range from a mild morbilliform rash (most common, see Figure 2.2-9) to the rare but life-threatening toxic epidermal necrolysis (TEN). Maintain a high suspicion for a cutaneous drug reaction in patients who are hospitalized and develop rashes. Drugs can cause **all four types of hypersensitivity reactions,** and the same drug may cause different types of reactions in different persons.



FIGURE 2.2-8. Urticaria (hives) and angioedema. This patient has urticaria occurring on the face, neck, and shoulders with orbital angioedema. (Reproduced with permission from Goldsmith LA et al. Fitzpatrick's Dermatology in General Medicine, 8th ed. New York, NY: McGraw-Hill; 2012.)

Q

A 23-year-old woman is seen for an itchy, linear rash on her right leg. She returned from a camping trip 4 days ago and denies using any new makeup, clothing, or jewelry. What features of this presentation favor a contact dermatitis?



FIGURE 2.2-9. Morbilliform rash. Morbilliform rash following drug administration. (Reproduced with permission from Longo DL et al. Harrison's Principles of Internal Medicine, 18th ed. New York, NY: McGraw-Hill; 2011.)

KEY FACT

Patients with drug eruptions often have eosinophilia and eosinophils on histopathology.

History/Pe

- Eruptions usually occur 7–14 days after exposure: **If a patient reacts within 1–2 days of starting a new drug, it is probably not the causative agent.**
- Eruptions are generally **widespread, relatively symmetric,** and **pruritic.**
- Most disappear within 1–2 weeks following removal of the offending agent.
- Extreme complications of drug eruptions include erythroderma, Stevens-Johnson syndrome (SJS), and TEN.

Diagnosis

Clinical impression. A skin biopsy may be helpful if the diagnosis is not clear.

Treatment

Discontinue the offending agent; treat symptoms with antihistamines and topical steroids to relieve pruritus.

ERYTHEMA MULTIFORME

EM is a cutaneous reaction pattern with classic **targetoid lesions** (see Figure 2.2-10) that has many triggers and is often recurrent.

KEY FACT

Erythema multiforme is often triggered by infections such as recurrent HSV or mycoplasma. Unlike SJS, it is not typically from a drug eruption.

History/Pe

- Typically, lesions start as erythematous macules that become centrally clear and then develop a blister. The **palms and soles are often affected.**
- In its minor form, the disease is uncomplicated and localized to the skin.
- **EM major involves mucous membranes.** It is a distinct entity from SJS, and there is no risk of progression to TEN.
- May have systemic symptoms, including fever, myalgias, arthralgias, and headache.

A

The asymmetric involvement of the rash, its linear arrangement (possibly from contact with a plant during the camping trip), and the time from exposure to rash presentation all point to contact dermatitis.

Diagnosis

Clinical. As opposed to SJS or TEN, in EM the **Nikolsky sign is negative.**



FIGURE 2.2-10. Erythema multiforme. (Reproduced with permission from Dr. Richard Usatine.)

Treatment

- Symptomatic treatment is all that is necessary; systemic corticosteroids are of no benefit.
- Minor cases can be treated with antipruritics; major cases should be treated as burns.

STEVENS-JOHNSON SYNDROME/TOXIC EPIDERMAL NECROLYSIS

SJS and TEN constitute two different points on the spectrum of **life-threatening exfoliative mucocutaneous diseases** that are often caused by a drug-induced immunologic reaction. **The epidermal separation of SJS involves < 10% of body surface area (BSA), whereas TEN involves > 30% of BSA.**

History/Pe

- Exam reveals severe mucosal erosions with widespread erythematous, dusky red or purpuric macules or atypical targetoid lesions (see Figure 2.2-11). The epidermal lesions often become confluent and show a ⊕ **Nikol-**



FIGURE 2.2-11. Toxic epidermal necrolysis. Note the diffuse erythematous bullae and areas of sloughing 2° to the full-thickness necrosis of the epidermis. (Reproduced with permission from Tintinalli JE et al. Tintinalli's Emergency Medicine: A Comprehensive Study Guide, 7th ed. New York, NY: McGraw-Hill; 2011.)

KEY FACT

Always include SJS and TEN in your differential diagnosis if a ⊕ Nikolsky's sign is present.

KEY FACT

Don't confuse SJS and TEN with SSSS. SSSS is usually seen in children < 6 years of age and has an infectious etiology. SJS/TEN is generally seen in adults and is usually caused by a drug reaction.

MNEMONIC

Causes of erythema nodosum—

NODOSUM:

NO cause (60% idiopathic)
Drugs: sulfa, iodide
Oral contraceptives
Sarcoidosis
Ulcerative colitis/Crohn disease
Microbiology (TB, leprosy, histoplasmosis, chronic infection)



FIGURE 2.2-12. Erythema nodosum. Erythematous plaques and nodules are commonly located on pretibial areas. Lesions are painful and indurated but heal spontaneously without ulceration. (Reproduced with permission from Hurwitz RM. Pathology of the Skin: Atlas of Clinical-Pathological Correlation, 2nd ed. Stamford, CT: Appleton & Lange; 1998.)

sky sign (separation of the superficial skin layers with slight rubbing) and epidermal detachment.
- Mucous membranes (eyes, mouth, and genitals) often become eroded and hemorrhagic.
- Associated with first-time exposure to drugs: sulfonamides, penicillin, seizure medications (phenytoin, carbamazepine), quinolones, cephalosporins, steroids, NSAIDs.

Diagnosis

- **SJS:** Biopsy shows **degeneration of the basal layer of the epidermis.**
- **TEN:** Biopsy shows **full-thickness eosinophilic epidermal necrosis.**
- Include staphylococcal scalded-skin syndrome (SSSS), graft-vs-host reaction (usually after bone marrow transplant), radiation therapy, and burns on the differential diagnosis.

Treatment

- High risk of mortality. **Early diagnosis and discontinuation of offending agent are critical** in improving survival.
- Patients have the **same complications as burn victims:** Thermoregulatory and electrolyte disturbances and 2° infections, so cover the skin and manage fluids and electrolytes.
- Data on pharmacologic therapy with steroids, cyclosporine and IVIG is mixed.

ERYTHEMA NODOSUM

A **panniculitis** (inflammatory process of the **subcutaneous adipose tissue**) triggered by infection (Streptococcus, Coccidioides, Yersinia, TB), drug reactions (sulfonamides, antibiotics, OCPs), and chronic inflammatory diseases (sarcoidosis, Crohn disease, ulcerative colitis, Behçet disease).

History/Pe

- **Painful, erythematous nodules** appear on the patient's **anterior shins** (see Figure 2.2-12) and slowly spread, turning brown or gray. Patients may present with fever and joint pain.
- Patients with erythema nodosum may have a false-⊕ VDRL (as in SLE).

Diagnosis

Clinical. Workup with an ASO titer, PPD in high-risk patients, a CXR to rule out sarcoidosis, or inflammatory bowel disease workup based on the patient's complaints.

Treatment

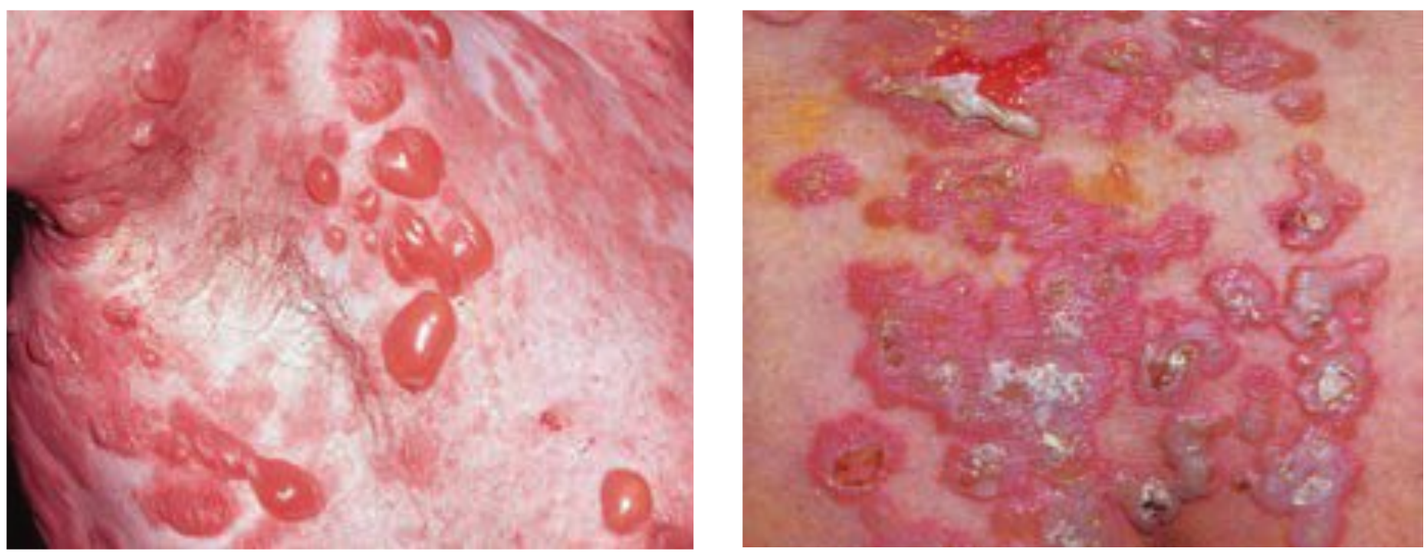
Investigate and treat the underlying disease. NSAIDs and cool compresses are helpful. Potassium iodide may be considered for persistent cases.

BULLOUS PEMPHIGOID/PEMPHIGUS VULGARIS

Table 2.2-3 contrasts the clinical features of bullous pemphigoid with those of pemphigus vulgaris. Figure 2.2-2 shows the location of antibodies.

TABLE 2.2-3. Acquired, Autoimmune Blistering Dermatoses

Variable	Bullous pemphigoid	Pemphigus vulgaris
Location of blisters	Basement membrane zone.	Intraepidermal.
Autoantibodies	Against hemidesmosomal proteins.	Anti-desmoglein; desmoglein is responsible for keratinocyte adhesion.
Blister appearance	Firm, stable blisters; may be preceded by urticaria (see Figure 2.2-13).	Erosions are more common than intact blisters because of the lack of keratinocyte adherence (see Figure 2.2-14).
Nikolsky sign	⊖	⊕
Mucosal involvement	Rare.	Common.
Patient age	Usually > 60 years of age.	Usually 40–60 years of age.
Associated medication triggers	Generally idiopathic.	ACEIs, penicillamine, phenobarbital, penicillin.
Mortality	Rare and milder course.	Possible.
Diagnosis	Clinical. Most accurate test: **skin biopsy with direct immunofluo escence,** and/or ELISA.	Same as that for bullous pemphigoid.
Treatment	Steroids (prednisone).	High-dose steroids (prednisone) + immunomodulatory therapy (azathioprine, mycophenolate mofetil, IVIG, rituximab).



A B

FIGURE 2.2-13. (A) Bullous pemphigoid and (B) pemphigus vulgaris. Multiple tense vesicles and bullae can be seen **(A).** Note the confluent, flaccid blisters and erosions, which are extremely painful. Mucous involvement is common **(B).** (Part A reproduced with permission from Wolff K, Johnson RA. Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology, 6th ed. New York, NY: McGraw-Hill; 2009. Part B reproduced with permission from Wolff K, Johnson RA. Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology, 6th ed. New York, NY: McGraw-Hill; 2009.)

Infectious Disease Manifestations of the Skin

VIRAL DISEASES

Herpes Simplex

Painful, recurrent vesicular eruption of the mucocutaneous surfaces due to infection with HSV. **HSV-1 usually produces oral-labial lesions, whereas HSV-2 usually causes genital lesions.** The virus spreads through epidermal cells, fusing them into **giant cells.** The local host inflammatory response causes erythema and swelling.

History/Pe

- The initial infection is by direct contact, after which the herpesvirus remains dormant in local nerve ganglia. **1° episodes are generally longer and more severe** than recurrences.
- Onset is preceded by prodromal tingling, burning, or pain but can also present with lymphadenopathy, fever, discomfort, malaise, and edema of involved tissue.
- Recurrences are limited to mucocutaneous areas innervated by the involved nerve.
  - **Recurrent oral herpes (HSV-1):** The common **"cold sore,"** or herpes labialis, which presents as a cluster of crusted vesicles on an erythematous base (see Figure 2.2-15A). Often triggered by sun and fever.
  - **Recurrent genital herpes (HSV-2):** Unilateral and characterized by a cluster of blisters on an erythematous base, but with less pain and systemic involvement than the 1° infection.

Diagnosis

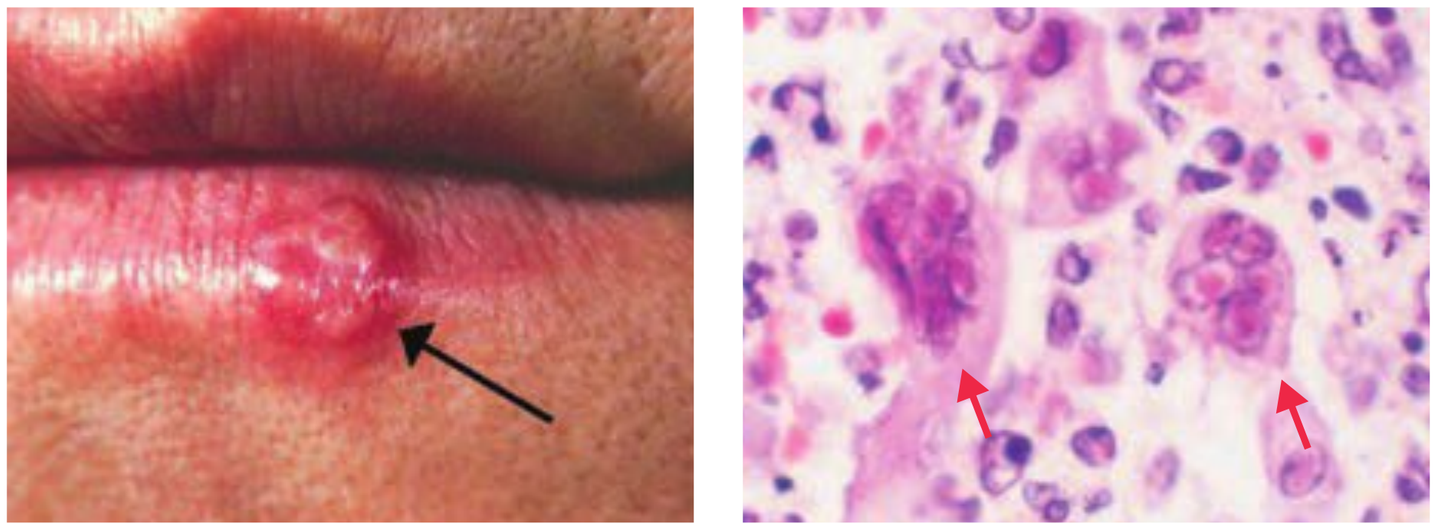
- Clinical. **Viral culture of lesion** is the most accurate test. Direct fluorescent antigen is the most rapid.
- Classic multinucleated **giant cells on Tzanck smear** (Figure 2.2-15B) support the diagnosis.

KEY FACT

Dermatitis herpetiformis (DH) has vesicles and erosions like herpes but is not caused by HSV. DH consists of pruritic papules, vesicles, bullae and erosions on the elbows (see Figure 2.2-14), knees, buttocks, neck, and scalp, and it is **associated with celiac disease** (15–25%). Treat with dapsone and a gluten-free diet.



FIGURE 2.2-14. Dermatitis herpetiformis. This disorder typically displays pruritic, grouped papulovesicles on elbows, knees, buttocks, and posterior scalp. Vesicles are often excoriated due to associated pruritus. (Reproduced with permission from Longo DL et al. Harrison's Principles of Internal Medicine, 18th ed. New York, NY: McGraw-Hill; 2011.)



A B

FIGURE 2.2-15. Herpes simplex. (A) Herpes labialis. **(B)** Positive Tzanck smear in genital herpes (HSV-2). Note multinucleated giant cells (arrows). (Part A reproduced with permission of the US Department of Health and Human Services and Dr. Herrmann. Part B used with permission from Yale Rosen.)

Treatment

- **First episode:** Immunocompetent patients with small lesions only need supportive therapy but **acyclovir/famciclovir/valacyclovir** may be given to speed healing and reduce shedding.
  - Immunocompromised patients or those with a severe painful outbreak should receive an **antiviral drug within 72 hours of the start** of the outbreak.
- **Recurrent episodes:** Minor lesions can be managed supportively. Acyclovir, famciclovir, or valacyclovir can be given during the episode to reduce healing time by ~ 2 days.
- **Severe frequent recurrences (more than six outbreaks per year):** Daily prophylaxis with acyclovir, famciclovir, or valacyclovir.
- In AIDS patients, HSV can persist, with ulcers remaining resistant to antiviral therapy. Symptomatic HSV infection lasting > 1 month can be considered an AIDS-defining illness.

KEY FACT

No multinucleated giant cells on Tzanck smear? Tzanck goodness it's not herpes!

Varicella-Zoster Virus (VZV)

VZV causes two different diseases, varicella and herpes zoster—with transmission occurring via respiratory droplet or by direct contact. VZV has an incubation period of 10–20 days, with contagion beginning 24 hours before the eruption appears and lasting until lesions have crusted.

History/Pe

- **Varicella:**
  - A prodrome of malaise, fever, headache, and myalgia occurs 24 hours before the rash.
  - Pruritic lesions appear in crops over 2–3 days, evolving from red macules to vesicles that then crust over.
  - At any given time, patients may have **all stages of lesions present.** The trunk, face, scalp, and mucous membranes are involved.
  - In adults, chickenpox is often more severe, with **systemic complications** such as **pneumonia** and **encephalitis.**
- **Zoster:**
  - Herpes zoster **(shingles)** represents the recurrence of VZV in a specific nerve, with lesions cropping up along the nerve's **dermatomal** distribution. Outbreaks are usually preceded by intense local pain followed by grouped blisters on an erythematous base (see Figure 2.2-16). Zoster can become disseminated in immunocompromised persons.
  - Older patients with zoster can develop **postherpetic neuralgia** (severe nerve pain that persists for months at the infection site).



FIGURE 2.2-16. Varicella zoster. The unilateral dermatomal distribution of the grouped vesicles on an erythematous base is characteristic. (Reproduced with permission from Wolff Ket al. Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology, 5th ed. New York, NY: McGraw-Hill; 2005.)

KEY FACT

Immunocompromised patients, cancer patients (especially those undergoing chemotherapy), the elderly, and severely stressed individuals are more susceptible to zoster infection.

Diagnosis

Clinical.

Treatment

- Varicella is self-limited in healthy children. A vaccine is available.
- **Adults should be treated with systemic acyclovir** to treat symptoms and prevent complications. **Pain control** with neuropathic agents (gabapentin, tricyclic antidepressants).
- **Postexposure prophylaxis:** Rarely needed as most patients in the United States have been vaccinated or had childhood varicella. If needed, immunocompromised individuals, pregnant women, and newborns should receive varicella-zoster immune globulin within 10 days of exposure. Immunocompetent adults should receive a varicella vaccine within 5 days of exposure.

Q

A 28-year-old black woman is seen by her physician for a new-onset, painful rash. She noticed the erythematous nodules on both lower legs 3 days ago. She has a history of uveitis. What is the next best step to identify the underlying cause of this rash?

KEY FACT

If you see giant molluscum contagiosum, think HIV or ↓ cellular immunity.



FIGURE 2.2-17. Molluscum contagiosum. (Used with permission from Dr. Richard Usatine.)

Molluscum Contagiosum

A **poxvirus infection** that is most common in young children and in **AIDS patients.** It is spread by direct skin-to-skin contact (sports, sex) or sharing infected clothing or towels.

History/PE

- Presents as **tiny flesh-colored dome-shaped waxy papules,** frequently with **central umbilication.** In children, lesions are found on the trunk, extremities, or face (see Figure 2.2-17). In adults, they are commonly found on the genitalia and in the perineal region. Typically spares palms and soles.
- **Lesions are asymptomatic** unless they become inflamed or irritated.

Diagnosis

Clinical. If the diagnosis is uncertain, most accurate test is the presence of **large inclusion or molluscum bodies** seen under the microscope.

Treatment

- Local destruction: curetting, freezing, or applying trichloroacetic acid to the lesions.
- In kids, lesions resolve spontaneously over months to years and are often left untreated.

Verrucae (Warts)

Warts are caused by **HPV** and can occur on skin, mucous membranes, and other epithelia. Although usually benign, **some subtypes of HPV (especially 16 and 18)** lead to **squamous malignancies**. Spread is by direct contact.

History/PE

- Common warts are most often seen on the hands, though they can occur anywhere.
- Classic genital warts (condyloma acuminatum, caused by HPV subtypes 6 and 11) are **cauliflower-like papules or plaques** appearing on the penis, the vulva, or the perianal region (see Figure 2.2-18).
- Mothers with genital HPV can transmit laryngeal warts to the infant by aspiration during delivery.



A B

FIGURE 2.2-18. Verrucae (warts). Caused by HPV. **(A)** Soft, tan-colored, cauliflower-like papules on hands. **(B)** Condyloma acuminatum on genitals. (Used with permission from Dr. Richard Usatine.)

A

A CXR to look for bilateral hilar adenopathy, which is suggestive of sarcoidosis. Erythema nodosum is the most common nonspecific cutaneous manifestation of sarcoidosis, after cutaneous sarcoidosis.

Diagnosis

- Clinical. Acetic acid turns lesions white and can be used to visualize mucosal lesions.
- Most accurate test is PCR of the lesion for HPV.

Treatment

Genital warts are treated locally: cryotherapy, podophyllin, trichloroacetic acid, imiquimod, or 5-FU. Cervical lesions are monitored for evidence of malignancy (see Gynecology chapter).

BACTERIAL INFECTIONS

See Figure 2.2-19.

Impetigo

Local infection of the **epidermis** that primarily occurs in children and is caused by both **group A streptococcal and staphylococcal** organisms. It is transmitted by direct contact. **Streptococcal impetigo can be complicated by acute streptococcal glomerulonephritis.**

History/Pe

- **Common type:** Pustules and **honey-colored crusts** on an erythematous base, often on the face around the mouth, nose, or ears (see Figure 2.2-20).
- **Bullous type:** Characterized by bulla in addition to crusts that can involve the acral surfaces. **Bullous impetigo is almost always caused by** S aureus and can evolve into SSSS.

Diagnosis

Clinical.

Treatment

Use antibiotics with antistaphylococcal activity based on severity and MRSA suspicion.



FIGURE 2.2-20. Impetigo. Dried pustules with a superficial golden-brown crust are most commonly found around the nose and mouth. (Reproduced with permission from Bondi EE. Dermatology: Diagnosis and Therapy, 1st ed. Stamford, CT: Appleton & Lange; 1991.)

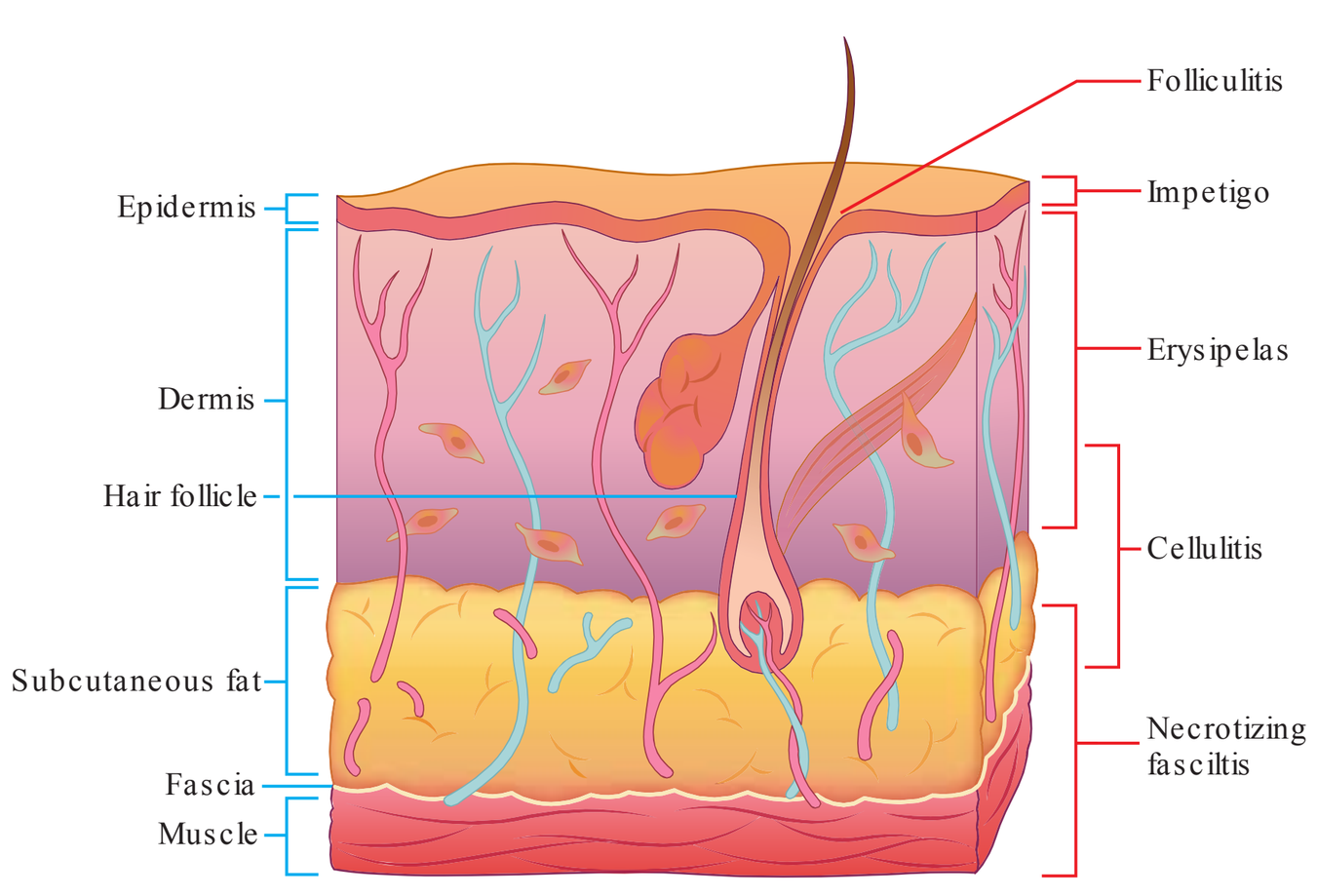


FIGURE 2.2-19. Skin layers (blue) and depths of infection (red).

KEY FACT

- **Scarlet fever:** "Sandpaper" rash or "sunburn with goose bumps" appearance; strawberry tongue. Caused by Streptococcus pyogenes. Treat with penicillin.
- Salmonella typhi: Small pink papules on the trunk ("rose spots") in groups of 10–20 plus fever and GI involvement. Treat with fluoroquinolones and third-generation cephalosporins. Consider cholecystectomy for chronic carrier state.



FIGURE 2.2-21. Erysipelas of the face. (Reproduced from Goldsmith LA et al. Fitzpatrick's Dermatology in General Medicine, 8th ed. New York, NY: McGraw-Hill; 2012.)

KEY FACT

Ludwig angina is a bilateral cellulitis of the submental, submaxillary, and sublingual spaces that usually results from an infected tooth. It presents with dysphagia, drooling, fever, and a red, warm mouth, and can lead to death from asphyxiation.

- **Mild localized disease: Topical antibiotics** (mupirocin) are sufficient.
- **Severe disease (non-MRSA):** Oral **cephalexin, dicloxacillin,** or erythromycin.
- **Severe disease (MRSA likely):** Oral **trimethoprim-sulfamethoxazole,** clindamycin, or doxycycline.

Cellulitis

A deeper skin infection involving **dermis and subcutaneous tissue.** Commonly caused by **staphylococci** or **group A streptococci** originating from damaged skin or a systemic source. **Community-acquired MRSA** is an increasingly common cause of purulent cellulitis. Risk factors include diabetes, IV drug use, venous stasis, and immune compromise.

History/Pe

- Presents with **red, hot, swollen, tender skin.** Fever and chills are common.
- **Erysipelas** is a type of cellulitis usually caused by streptococcus that is confined to the dermis and lymphatic tissue, creating a characteristically **raised, indurated, well-demarcated, erythematous** area of skin (see Figure 2.2-21).

Diagnosis

- Clinical. Cultures may aid in diagnosis and help determine antibiotic sensitivities for treatment if pus or sepsis is present.
- Rule out abscess, osteomyelitis, and necrotizing fasciitis.

Treatment

- Topical antibiotics are ineffective due to depth of infection.
- Use 5–10 days of oral antibiotics. IV antibiotics are used if there is evidence of systemic toxicity, comorbid conditions, diabetes mellitus (DM), extremes of age, or hand or orbital involvement. Antibiotic choices similar to impetigo.

Necrotizing Fasciitis

Deep infection along a **fascial plane** causing severe pain followed by anesthesia. It is usually caused by a **mixed infection of anaerobic and aerobic bacteria that includes** S aureus, Escherichia coli, **and** Clostridium perfringens. Ten percent of cases are caused by S pyogenes. A history of trauma or recent surgery to the affected area is sometimes elicited.

History/Pe

- Acute onset of pain and swelling progressing to anesthesia at the site of trauma or surgery.
- An area of **erythema quickly spreads over the course of hours to days.** Margins move out into normal skin, and skin becomes dusky or purplish near the site of insult, ultimately leading to **necrosis** (see Figure 2.2-22).
- If a necrotic area is open, gloved fingers can easily pass between two layers to reveal yellow-green necrotic fascia (infection spreads quickly in deep fascia).
- Important signs of tissue necrosis are **gas production** (**crepitus** on physical exam), **a putrid discharge, bullae, severe pain,** lack of inflammatory signs, and intravascular volume loss.



FIGURE 2.2-22. Necrotizing fasciitis of the lower extremity. Patient presented with hypotension due to late necrotizing fasciitis and myositis due to β-hemolytic streptococcal infection. (Reproduced with permission from Brunicardi FC et al. Schwartz's Principles of Surgery, 9th ed. New York, NY: McGraw-Hill; 2010.)

Diagnosis

Strong suspicion of necrotizing fasciitis based on clinical exam and imaging (showing gas in soft tissue) requires **immediate surgical exploration and debridement;** tissue culture helps determine the organisms involved.

Treatment

- A **surgical emergency:** Early and aggressive surgical debridement is critical.
- In most cases, **broad-spectrum coverage** is necessary. If Streptococcus is the principal organism involved, penicillin G is the drug of choice. Clindamycin is second line and also used to decrease toxin production by bacteria. For anaerobic coverage, give metronidazole or a third-generation cephalosporin.

KEY FACT

Fournier gangrene is a form of necrotizing fasciitis that is localized to the genital and perineal area.

Folliculitis

Inflammation and/or infection of a hair follicle. Typically caused by infection with Staphylococcus, Streptococcus, and gram-⊖ bacteria. Occasionally can be caused by yeast such as Candida albicans or Malassezia furfur. Can occur on **any body area with follicles.**

KEY FACT

Pseudomonas aeruginosa infection leads to "hot tub folliculitis."

History/Pe

- Presents as a tiny pustule at the opening of a hair follicle with a hair penetrating it. When the infection is deeper, a **furuncle,** or hair follicle abscess, develops. Furuncles may disseminate to adjacent follicles to form a **carbuncle** (see Figure 2.2-23).
- Patients with diabetes or immunosuppression are at ↑ risk. Eosinophilic folliculitis can occur in AIDS patients, in whom the disease is intensely pruritic and resistant to therapy.

Q

A 7-year-old girl presents with fever, sore throat, and a facial rash. Physical examination reveals an erythematous pharynx without exudates and a red, painful patch on the child's cheek that the mother notes has been expanding. What is the appropriate therapy?

Diagnosis

Clinical. KOH prep or biopsy may be needed if fungus or eosinophilic folliculitis is suspected.



FIGURE 2.2-23. Carbuncle due to methicillin-sensitive S aureus. A very large, inflammatory plaque studded with pustules, draining pus, on the nape of the neck. Infection extends down to the fascia and has formed from a confluence of many furuncles. (Reproduced with permission from Wolff Ket al. Fitzpatrick's Color Atlas &Synopsis of Clinical Dermatology, 7th ed. New York, NY, McGraw-Hill; 2013.)

Tr ea Tmen T

Topical antibiotics (mupirocin) treat mild superficial disease. More severe disease is treated similarly to impetigo, with cephalexin or cloxacillin orally, escalating to clindamycin if MRSA is suspected.

Acne Vulgaris

A skin disease common among adolescents. The pathogenesis involves **hormonal activation of sebaceous glands,** the development of the comedo **(plugged pilosebaceous follicle),** and involvement of Propionibacterium acnes **in the follicle,** causing inflammation. Acne lesions can be caused by medications (lithium, corticosteroids) or by topical occlusion (cosmetics).

His To r y/Pe

- There are three stages of acne lesions:
  - **Comedonal:** Open **("blackheads")** or closed **("whiteheads")** comedones.
  - **Inflammatory:** The comedones rupture, creating inflammatory papules, pustules, nodules, and cysts.
  - **Scar:** May develop as inflammation heals. Picking at lesions exacerbates scarring.
- Acne develops at puberty and typically persists for several years. Male adolescents are more likely to have severe cystic acne than are their female contemporaries.
- Women in their 20s can have a variant that **flares cyclically with menstruation,** with fewer comedones but more painful lesions on the chin.

KEY FACT

Ironically, erythromycin does **not** cause erythema with sun exposure. It is tetracycline and doxycycline that can cause photosensitivity!

A

This child has erysipelas, a rash commonly caused by group A streptococci. It can present as a small red patch on the cheek or extremities that turns into a painful, shiny red plaque. Patients often have a history of chronic cutaneous ulcers, lymphedema, or pharyngitis. Treat with penicillin.

Diagnosis

Clinical.

Treatment

- **Mild–moderate acne: Topical retinoids are the most effective topical agent** for comedonal acne. Topical benzoyl peroxide kills P acnes. Consider adding a topical antibiotic (clindamycin, erythromycin) if response to other topicals is inadequate.
- **Moderate–severe acne:** In addition to topical treatment as above, add oral antibiotics such as **doxycycline or minocycline.** When acne is severe and all treatments are failing, **oral retinoids (isotretinoin)** are the most effective treatment. All other medications are stopped.
  - Isotretinoin is a **teratogen** and **elevates LFTs.** Patients require **periodic blood tests to check LFTs, cholesterol, and triglycerides.**

KEY FACT

General progression of acne treatment based on severity: **topical** benzoyl peroxide/retinoid/antibiotic → **oral antibiotic** → oral isotretinoin.

Pilonidal Cysts

Abscesses in the sacrococcygeal region. Not all contain hair or are true cysts. The condition is thought to start as a folliculitis that becomes an abscess complicated by perineal microbes, especially Bacteroides, as a result of repetitive trauma. Most common in 20- to 40-year-old men.

History/Pe

- Presents as an abscess at the natal cleft that can be tender, fluctuant, and warm; sometimes associated with purulent drainage or cellulitis. Systemic symptoms are uncommon, but cysts can develop into perianal fistulas.
- Risk factors include deep and hairy natal clefts, obesity, and a sedentary lifestyle.

Diagnosis

Clinical.

Treatment

- Treat with **incision and drainage** of the abscess followed by sterile packing of the wound.
- Good local hygiene and shaving of the sacrococcygeal skin can help prevent recurrence.

KEY FACT

Antibiotics are not needed for pilonidal cysts unless cellulitis is present; if antibiotics are prescribed, both aerobic and anaerobic coverage is required.

FUNGAL INFECTIONS

Tinea Versicolor

Caused by Malassezia furfur, a yeast that is part of normal skin flora. Humid and sweaty conditions as well as oily skin can make the organism pathogenic. Cushing syndrome and immunosuppression are also risk factors.

History/Pe

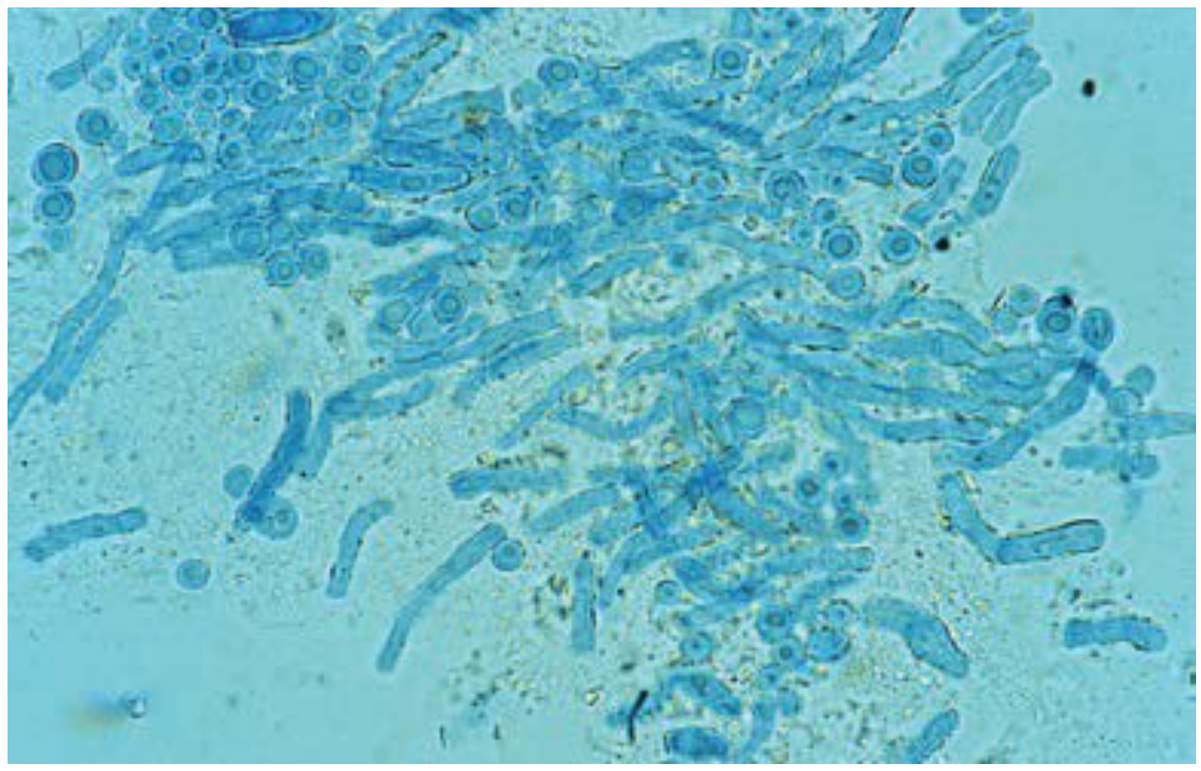
- Presents with small scaly patches of **varying color** on the chest or back (see Figure 2.2-24A).
- Patches can be **hypopigmented** as a result of interference with melanin production, or **hyperpigmented/pink** possibly due to inflammation.

Diagnosis

Clinical. Best initial test is a KOH preparation of the scale revealing **"spaghetti and meatballs"** pattern of hyphae and spores (see Figure 2.2-24B).



A



B

FIGURE 2.2-24. Tinea versicolor. (A) Note the discrete, hypopigmented patches extensively involving the patient's back. Tinea versicolor may also present as hyperpigmented macules or patches in some individuals. **(B)** KOH preparation shows the characteristic "spaghetti and meatballs" pattern. (Part A reproduced with permission from Tintinalli JE et al. Tintinalli's Emergency Medicine: A Comprehensive Study Guide, 7th ed. New York, NY: McGraw-Hill; 2011. Part B reproduced with permission from Wolff K et al. Fitzpatrick's Dermatology in General Medicine, 7th ed. New York, NY: McGraw-Hill; 2008.)

Treatment

Treat lesions with topical **ketoconazole or selenium sulfide.**

Candidiasis

"Yeast infection" or "thrush," candidiasis can be caused by any Candida species but is most commonly caused by C albicans. In immune-competent patients, it typically presents as a superficial infection of the skin or mucous membranes **in moist areas such as the groin, skin folds, axillae, the vagina, and below the breasts.** Oral thrush is common in infancy, but in adults it is often **a sign of a weakened immune system.**

History/Pe

- Patients often have **history of antibiotic or steroid use, diabetes, immunocompromise.**
- **Oral candidiasis:** Presents with painless white plaques that **can be easily scraped off.**
- **Candidiasis of the skin:** Presents as markedly erythematous patches with occasional erosions and **smaller satellite lesions** (see Figure 2.2-25) seen nearby, often in skin folds. In infants, infection is often seen in the diaper area and along the inguinal folds.

Diagnosis

Clinical. Best initial test is a KOH preparation of a scraping of the affected area. KOH dissolves the skin cells but leaves the Candida untouched such that **candidal spores and pseudohyphae** become visible. Most accurate test is a fungal culture.

Treatment

- **Oral candidiasis:** Oral fluconazole tablets; nystatin swish and swallow, clotrimazole troches.



FIGURE 2.2-25. Cutaneous candidiasis with satellite lesions. (Reproduced with permission from Goldsmith LA et al. Fitzpatrick's Dermatology in General Medicine, 8th ed. New York, NY: McGraw-Hill; 2012.)

- **Superficial (skin) candidiasis:** Topical antifungals; keep skin clean and dry.
- **Diaper rash:** Topical nystatin.

Dermatophyte Infections

Dermatophytes only live in **tissues with keratin (skin, nails, and hair)** and are a common cause of infection. **Causative organisms include** Trichophyton **(most common),** Microsporum, **and** Epidermophyton species. Risk factors include diabetes, ↓ peripheral circulation, immune compromise, and chronic maceration of skin (from athletic activities).

History/Pe

Varies according to subtype:

- **Tinea corporis:** Scaly, pruritic eruption with a sharp, irregular border, often with central clearing (see Figure 2.2-26). Can be seen in immunocompromised patients or in children following contact with infected pets.
- **Tinea pedis/manuum:** (see Figure 2.2-27A): Presents as chronic interdigital scaling with erosions between the toes **("athlete's foot")** or as a **thickened, scaly skin on the soles** (moccasin distribution). In addition, involvement of one hand is typical in the "one hand two feet syndrome."



FIGURE 2.2-26. Tinea corporis. Note the "ringworm-like" rash with a scaly, erythematous, distinct border and central clearing. (Reproduced with permission from Wolff K et al. Fitzpatrick's Dermatology in General Medicine, 7th ed. New York, NY: McGraw-Hill; 2008.)



A B C

FIGURE 2.2-27. Cutaneous mycoses. (A) Tinea pedis; **(B)** tinea cruris; **(C)** tinea capitis. (Used with permission from Dr. Richard Usatine.)

- **Tinea cruris ("jock itch")** (see Figure 2.2-27B): A fungal infection of the groin (typically sparing the scrotum) that is usually associated with tinea pedis.
- **Tinea capitis** (see Figure 2.2-27C): A fungal scalp infection causing scaling and hair loss. A large inflammatory boggy mass caused by tinea capitis is called a **kerion.**

Diagnosis

Clinical. Best initial test: **KOH showing hyphae.** Most accurate: Fungal culture.

Treatment

Start with topical antifungals; escalate to oral if infection is widespread or unresponsive to topicals. **Tinea capitis must be treated with oral medications** to penetrate into hair follicles; oral treatment should also be considered in immunocompromised patients.

PARASITIC INFECTIONS

Lice

Lice live off blood and on specific parts of the body, depending on their species (head lice, body lice, pubic lice). Lice are spread through body contact or by the sharing of bedclothes and other garments or hair accessories. They secrete local toxins that lead to pruritus.

History/Pe

- Patients with lice often experience severe pruritus, and 2° bacterial infection of the excoriations is a risk. **Classroom epidemics** of head lice are common.
- Body lice are seen in people with inadequate hygiene or in those with crowded living conditions. Pubic lice (called "crabs" because of their squat, crablike body shape) contain anticoagulant in their saliva, so their bites often turn blue.

Diagnosis

Lice and their eggs (nits) can be seen on hairs or in clothes with the **naked eye.**

Treatment

- **Head lice:** Treat with topical permethrin, pyrethrin, benzyl alcohol, and mechanical removal.
- **Body lice:** Wash body, clothes, and bedding thoroughly. Rarely, topical permethrin is needed.
- **Pubic lice:** Treat with the same medications as for head lice.

Scabies

Caused by Sarcoptes scabiei. The burrowing of this arthropod into the epidermis leads to **pruritus** that ↑ in intensity once an allergy to the mite or its products develops. 2° bacterial infections due to scratching are common. Scabies mites are spread through close contact.

History/Pe

- Patients present with intense pruritus, especially at **night and after hot showers,** and erythematous papules with **linear tracks, representing the burrows** of the mite.
- The most commonly affected sites are the skin folds of the hands (often includes the **interdigital finger webs**), wrists, axillae, and genitals.

Diagnosis

A history of pruritus in several family members is suggestive. The mite may be identifiable by scraping an intact tunnel and looking **under the microscope.**

Treatment

- Patients should be treated with 5% **permethrin from the neck down (head to toe for infants),** and their contacts should be treated as well. Oral **ivermectin** is also effective.
- Pruritus can persist up to 2 weeks after treatment.
- Clothes and bedding should be thoroughly washed as for lice.

KEY FACT

Lice can be seen with the naked eye. Scabies are too small and have to be identified with a microscope / dermatoscope.

Ischemic Disorders of the Skin

DECUBITUS ULCERS

Result from ischemic necrosis following **continuous pressure on an area of skin** that restricts microcirculation.

History/Pe

Ulcers are commonly seen in **bedridden patients** who lie in the same spot for too long. An underlying bony prominence or lack of fat ↑ the likelihood of ulcer formation **(sacrum, heels).** Patients lacking mobility or cutaneous sensation are also at ↑ risk. Incontinence of urine or stool may macerate the skin, facilitating ulceration.

Diagnosis

Clinical.

Treatment

- **Prevention is key:** Routinely move bedridden patients; special beds can distribute pressure.
- If an ulcer develops, low-grade lesions can be treated with routine wound care, including hydrocolloid dressings. High-grade lesions require **surgical debridement.**

GANGRENE

Necrosis of body tissue. There are three subtypes: **dry, wet,** and **gas.**

- **Dry gangrene:** Due to insufficient blood flow to tissue, typically from **atherosclerosis.**
- **Wet gangrene:** Involves **bacterial infection,** usually with skin flora.
- **Gas gangrene:** Due to C perfringens **infection.**

Q 1

A 42-year-old man is admitted for cellulitis after injuring his leg while swimming. He is febrile and has a well-demarcated area of erythema on the anterior aspect of his right knee. Antibiotics are started. Six hours later, the patient is in excruciating pain. The erythema has spread circumferentially around the knee, and the anterior aspect of the knee now has a purplish hue. What is the next best step?

Q 2

A 17-year-old girl has been followed by a dermatologist for severe cystic acne that has been refractory to both topical and systemic antibiotics. She inquires about isotretinoin (Accutane). Given this drug's potentially hazardous side effects, what laboratory tests would have to be performed monthly if this patient were to be placed on isotretinoin?

History/Pe

- **Dry gangrene:** Early signs are a dull ache, cold, and pallor of the flesh. As necrosis sets in, the tissue (toes, fingers) becomes bluish-black, dry, and shriveled. Diabetes, vasculopathy, and smoking are risk factors.
- **Wet gangrene:** The tissue appears bruised, swollen, or blistered with pus.
- **Gas gangrene:** Occurs at sites of large trauma/surgery compromising blood flow to a region, bringing about an anaerobic environment. Bacteria rapidly destroy tissue, producing gas that separates healthy tissue and exposes it to infection. Associated with **dirty wounds** contaminated with dirt or bowel/fecal matter. Subcutaneous injection of black tar heroin is a risk factor. Presents with swelling and pale or dark-red skin around the injury. **A medical emergency.**

Diagnosis

Clinical. Air in soft tissue on x-ray film is very suggestive (see Figure 2.2-28).

Treatment

- Surgical **debridement,** with amputation if necessary, is the mainstay of treatment. **Antibiotics alone do not suffice** by virtue of inadequate blood flow, but they should be given as an adjuvant to surgery.
- Hyperbaric oxygen (toxic to the anaerobic C perfringens) can be used **after debridement** to help with treatment.

Miscellaneous Skin Disorders

ACANTHOSIS NIGRICANS

- A condition in which the skin in the **intertriginous zones** (**neck folds,** genitals, axillae) is hyperkeratotic and **hyperpigmented with a velvety appearance** (see Figure 2.2-29).

1 **A**

Emergent surgical consult for debridement given the clinical suspicion for necrotizing fasciitis, a surgical emergency.

2 **A**

Serum or urine β-human chorionic gonadotrophin (to rule out pregnancy), LFTs, cholesterol, and triglycerides.



FIGURE 2.2-28. Gas gangrene. X-ray film of foot showing gas tracking through soft tissues. (Reproduced with permission from Tintinalli JE et al. Tintinalli's Emergency Medicine: A Comprehensive Study Guide, 7th ed. New York, NY: McGraw-Hill; 2011.)

- Associated with DM, Cushing disease, polycystic ovarian syndrome, and obesity. May also be a paraneoplastic sign of underlying adenocarcinoma (usually GI).
- **Tx:** Typically not treated. Encourage weight loss.



FIGURE 2.2-29. Acanthosis nigricans. Velvety, dark-brown epidermal thickening of the armpit is seen with prominent skin fold and feathered edges. (Reproduced with permission from Wolff K, Johnson RA, Saavedra AP. Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology, 7th ed. New York, NY: McGraw-Hill; 2013.)

LICHEN PLANUS

- A self-limited, recurrent, or chronic inflammatory disease affecting the skin, oral mucosa, and genitalia. Lesions classically described using the **6 P's (planar, purple, polygonal, pruritic, papules, and plaques).** It may be induced by drugs (thiazides, quinines, β-blockers) and is associated with HCV infection.
- **Hx/PE:** Presents with **violaceous, flat-topped, polygonal papules** (see Figure 2.2-30). **Wickham striae (lacy white lines) may be present on the lesion.** Lesions may demonstrate prominent **Koebner phenomena** (lesions that appear at the site of trauma).
- **Tx:** Mild cases are treated with **topical corticosteroids.** For severe disease, systemic corticosteroids and phototherapy may be used.

KEY FACT

Lichen planus is the "6P" disease: **P**ruritic, **P**urple, **P**olygonal, **P**lanar, **P**apules, **P**laques.



FIGURE 2.2-30. Lichen planus. Flat-topped, polygonal, sharply defined papules of violaceous color are grouped and confluent. The surface is shiny and reveals fine white lines (Wickham striae). (Reproduced with permission from Wolff Ket al. Fitzpatrick's Dermatology in General Medicine, 7th ed. New York, NY: McGraw-Hill; 2008.)

ROSACEA

- A chronic disorder of pilosebaceous units whose etiology is unclear. Early in the disease, **central facial erythema** is seen with **telangiectasias.** Later, papules and pustules may develop. Longstanding facial rosacea may lead to severe overgrowth of nasal connective tissue known as **rhinophyma** (see Figure 2.2-31). Ocular rosacea can predispose to blepharitis, stye and chalazion formation.



FIGURE 2.2-31. Rhinophyma. (Reproduced with permission from Wolff Ket al. Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology, 7th ed. New York, NY: McGraw-Hill; 2008.)

- **Hx/PE:**
  - Patients are **middle-aged with fair skin** and often have an **abnormal flushing** response to hot drinks, spicy foods, alcohol, sun. There is a female predominance.
  - Can be confused with acne but is not follicular in origin and involves an older age group.
- **Tx:** Topical **metronidazole.** For severe or ocular disease, oral doxycycline is used.

PITYRIASIS ROSEA

An acute dermatitis of unknown etiology that has been hypothesized to represent a reaction to a **viral infection with human herpesvirus (HHV) 7** because it tends to occur in mini-epidemics among young adults.

- **Hx/PE:**
  - Initial lesion is classically a **herald patch** that is erythematous with a peripheral scale.
  - Days to weeks later, a 2° eruption appears: multiple scaling papules and plaques with a fine **"cigarette paper"** scale (see Figure 2.2-32). Papules are arranged along skin lines, giving a classic **"Christmas tree" pattern** on the patient's back.
- **Dx: Clinical.** Confirm with KOH exam to rule out fungus (the herald patch may be mistaken for tinea corporis). Consider testing for secondary syphilis, which can present similarly.
- **Tx:** Rash **heals in 6–8 weeks without any treatment.** Supportive therapy to manage symptoms includes skin lubrication, antipruritics, and antihistamines.

KEY FACT

Pityriasis rosea spares palms and soles, whereas 2° syphilis does not.

VITILIGO

Acquired loss of function or absence of melanocytes leading to distinct areas of depigmentation. Probably 2° to autoimmune disease.



FIGURE 2.2-32. Pityriasis rosea. The round to oval erythematous plaques are often covered with a fine white scale ("cigarette paper") and are often found on the trunk and proximal extremities. Plaques are often preceded by a larger herald patch (inset). (Reproduced with permission from Tintinalli JE et al. Tintinalli's Emergency Medicine: A Comprehensive Study Guide, 7th ed. New York, NY: McGraw-Hill; 2011.)

- **Hx/PE: sharply demarcated, depigmented macules or patches** on otherwise normal skin, often on the hands, face, or genitalia (see Figure 2.2-33). Vitiligo can present at any age and vary from small areas of involvement with or without progression to large areas of depigmentation.
- **Dx:** Many patients have **serologic markers of autoimmune disease** (eg, antithyroid antibodies, DM, pernicious anemia) and occasionally present with these diseases.
- **Tx: Topical steroids,** tacrolimus ointment, UV and laser therapy are used. Sunscreen prevents burns. Cover-up makeup can help with cosmetic concerns.



FIGURE 2.2-33. Vitiligo of the hands. (Used with permission from Dr. Richard Usatine.)

EYELID LESIONS

- **Xanthelasma:** Soft and **yellow** plaques seen on the medial aspects of the eyelids bilaterally, associated with hyperlipidemia and 1° biliary cirrhosis.
- **Hordeolum: Painful** acute eyelid gland infection (stye), usually due to S aureus and located on the edge of the lid.
- **Chalazion:** Chronic inflammatory **painless** cyst due to a blocked eyelid gland.

Neoplasms of the Skin

SEBORRHEIC KERATOSIS

A very common skin tumor that appears in almost all people after age 40. The etiology is unknown. Lesions have no malignant potential (see Figure 2.2-34).

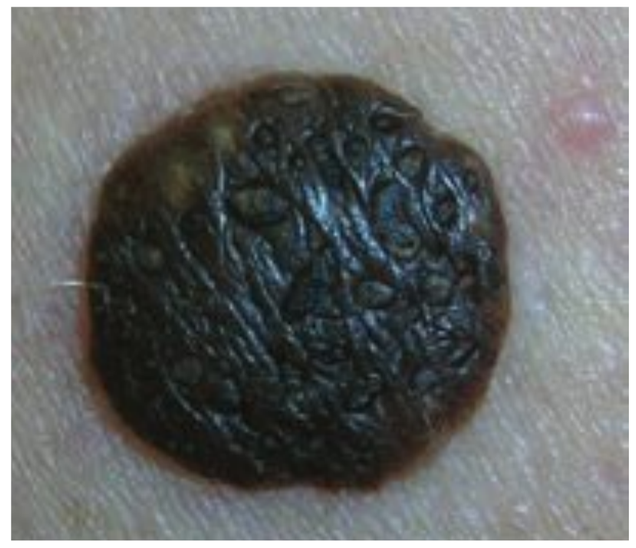


FIGURE 2.2-34. Seborrheic keratosis. (Used with permission from Dr. Richard Usatine.)

History/Pe

- Present as exophytic, waxy brown papules and plaques with superficial keratin cysts (see Figure 2.2-34). Lesions may appear in great numbers and **have a "stuck on" appearance.**
- Lesions can become irritated either spontaneously or by external trauma.

Diagnosis

Clinical. As some may appear similar to melanoma, a biopsy may be prudent in these cases.

Treatment

Cryotherapy, shave excision or curettage.



FIGURE 2.2-35. Actinic keratosis. The discrete patch above has an erythematous base and a rough white scale. (Reproduced with permission from Hurwitz RM. Pathology of the Skin: Atlas of Clinical-Pathological Correlation, 2nd ed. Stamford, CT: Appleton & Lange; 1998.)

ACTINIC KERATOSIS

Flat areas of erythema and scale caused by exposure to the sun. **These lesions should be treated to prevent the possible transformation into squamous cell carcinoma.**

History/Pe

Lesions appear on **sun-exposed areas** (face, arms) and primarily affect older patients, who often have multiple such lesions. They are **erythematous with a light scale** that can become thick and crusted (see Figure 2.2-35).

Q

A 72-year-old man presents to a new internist after moving to Florida. The internist notes a chronic wound on the patient's right lower leg. The patient states that the wound followed an episode of cellulitis and has been present for 3 years. What is the next best step?

Diagnosis

Clinical.

Treatment

Cryosurgery, topical 5-FU, or topical imiquimod can be used to destroy the lesion. If carcinoma is suspected, biopsy followed by excision or curettage is appropriate. Patients should be advised to use sun protection.

CUTANEOUS SQUAMOUS CELL CARCINOMA

The second most common skin cancer, with locally destructive effects as well as the potential for **metastasis and death. Sun exposure** is the most common causative factor, but exposure to **chemical carcinogens,** prior **radiation** therapy, sites of **burns or chronic trauma** (as in draining infectious sinuses in osteomyelitis), and chronic immunosuppression (as in transplant recipients) also predispose patients to developing SCC.



FIGURE 2.2-36. Squamous cell carcinoma. Note the crusting and ulceration of this erythematous plaque. Most lesions are exophytic nodules with erosion or ulceration. (Reproduced with permission from Hurwitz RM. Pathology of the Skin: Atlas of Clinical-Pathological Correlation, 2nd ed. Stamford, CT: Appleton & Lange; 1998.)

History/Pe

- SCCs have many forms, and a single patient will often have multiple variants.
- Most SCCs occur in older adults with sun-damaged skin, arising from actinic keratoses, presenting as erythematous, **ulcerated** papule or nodule (see Figure 2.2-36).
- **Marjolin's ulcer** is a type of rare SCC that arises in sites of scars, burns or ulcers.
- **Arsenic exposure** is a rare cause of multiple SCCs in a **palmoplantar distribution.**
- SCCs from actinic keratoses rarely metastasize, but those that arise on lips and ulcers are more likely to do so. SCC occurs on the lower lip more commonly than basal cell carcinoma.

Diagnosis

Clinical. Confirm with shave biopsy.

Treatment

Surgical excision or **Mohs surgery** (very thin slices are excised and examined with a microscope via frozen section). Lesions with high metastatic potential may need radiation or chemotherapy.

BASAL CELL CARCINOMA

The most common malignant skin cancer, BCC is slow growing and locally destructive but has **virtually no metastatic potential. Cumulative sun** exposure is the main risk factor. Most lesions appear on the face or other sun-exposed areas. Multiple BCCs appearing early in life and on non-sun-exposed areas are suggestive of **inherited basal cell nevus syndrome.**

A

Perform a biopsy on the lesion to rule out SCC.

History/Pe

There are many types of BCC with varying degrees of pigmentation, ulceration, and depth of growth (see Figure 2.2-37). Nodular, superficial, and sclerosing are the three main types.

Diagnosis

Clinical. Confirm with shave biopsy.

Treatment

Excision via curettage, cautery, cryotherapy, superficial radiation, and Mohs surgery.

MELANOMA

The most common life-threatening dermatologic disease. Risk factors include **fair skin and a tendency to burn; intense bursts of sun exposure** (especially in childhood and with intermittent exposure); and the presence of **large congenital melanocytic nevi, an ↑ number of nevi, or dysplastic nevi.** Immunosuppression also ↑ risk. Some patients inherit a predisposition to melanoma with the **familial atypical mole and melanoma (FAM-M) syndrome.** There are several subtypes (see Table 2.2-4).

History/Pe

- Malignant melanomas begin in the epidermal basal layer, where melanocytes are found.
- Malignant melanomas may metastasize **anywhere in the body** (lung, liver, brain, fat, etc). Three to 5% of patients with metastatic melanoma have no known 1° lesion.

Diagnosis

- Early recognition and treatment are essential. Screening exams using the **ABCDE criteria,** and dermoscopy may detect melanoma early when it is curable (see Figure 2.2-38). An **excisional biopsy** should be performed on any suspicious lesion. **Malignancy is determined histologically.**
- **Pruritus** in a changing skin lesion is a suspicious feature for malignant change.
- Malignant melanomas are staged by Breslow thickness (depth of invasion in millimeters) and by tumor-node-metastasis **(TNM) staging.** Ulceration is a poor prognostic sign.

TABLE 2.2-4. Types of Melanoma

type	preSentation
Superficial spreading	60% of all melanomas. Can occur at any age but is seen in young adults. Often presents on the trunk in men and on the legs in women. A prolonged horizontal growth allows for early diagnosis, when it is still confined o the epidermis.
Nodular	Lesions have a rapid vertical growth phase and appear as a fast-growing reddish-brown nodule with ulceration.
Acral lentiginous	Begins on the palms, soles, and nailbed as a slowly spreading, pigmented patch. Most commonly seen in Asians and blacks.
Lentigo maligna	Arises in a solar lentigo. Usually found on sun-damaged skin of the face.
Amelanotic	Presents as a lesion without clinical pigmentation. Difficult o identify. This variant of melanoma can be further classified i to any of the above types.

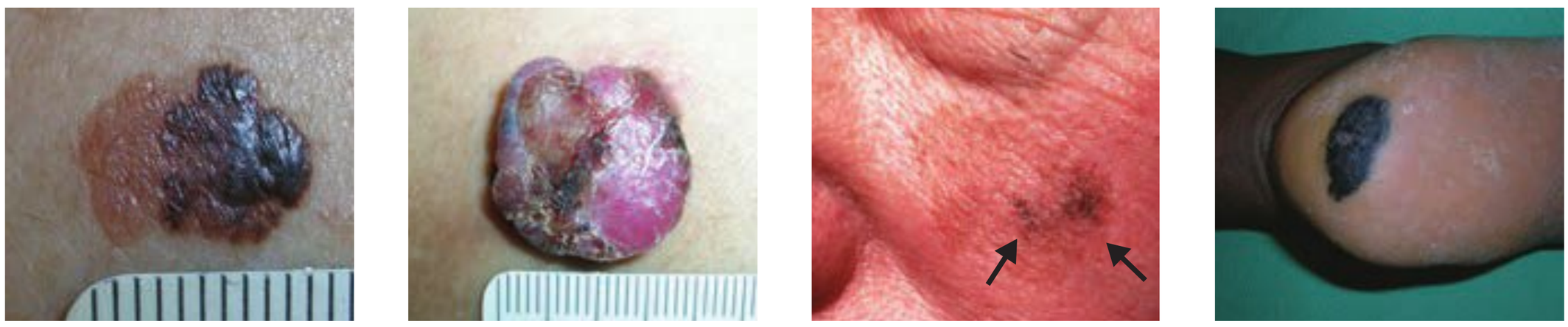


FIGURE 2.2-37. Nodular basal cell carcinoma. A smooth, pearly nodule with telangiectasias. (Reproduced with permission from Wolff K et al. Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology, 5th ed. New York, NY: McGraw-Hill; 2005.)

MNEMONIC

The ABCDEs of melanoma—

Asymmetric
Irregular **B**order
Variations in **C**olor
Diameter > 6 mm
Evolution: changing or new lesions



A B C D

FIGURE 2.2-38. Melanoma. (A) Superficial spreading; **(B)** nodular; **(C)** lentigo; **(D)** acral. (Used with permission from Dr. Richard Usatine.)

Treatment

- Lesions confined to the skin are treated by **excision with margins.** Sentinel lymph node biopsy is useful for staging but does not ↑ survival. Chemotherapy, biologic and radiation therapy may be used for recurrent or metastatic melanoma.
- Patients with early melanoma are at low risk for recurrence but are at high risk for the development of **subsequent melanomas. More advanced melanomas may recur or metastasize at a higher rate. Patient surveillance** is thus essential.

KAPOSI SARCOMA

A vascular proliferative disease that has been attributed to a herpesvirus, HHV-8, which is also called Kaposi sarcoma–associated herpesvirus (KSHV).

History/Pe

- Presents with multiple red to violaceous macules, papules, or nodules that can progress to plaques on the lower limbs, back, face, mouth, and genitalia (see Figure 2.2-39).
- Plaques can also be found in the GI tract and lung.
- **HIV-associated (epidemic) KS** is an aggressive form of the disease, and although less common since the advent of HAART, it remains the **most common HIV-associated malignancy.**

KEY FACT

Bacillary angiomatosis, caused by Bartonella henselae and Bartonella quintana, can mimic KS and should be excluded in suspected KS patients; erythromycin is the treatment of choice.



FIGURE 2.2-39. Kaposi sarcoma. Note the multiple violaceous papules on the neck, back, and face. (Reproduced with permission from Wolff K et al. Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology, 5th ed. New York, NY: McGraw-Hill; 2005.)

Diagnosis

Diagnosed by history, clinical impression, and histology.

Treatment

Start HAART therapy if patient is HIV positive. Small local lesions can be treated with radiation or cryotherapy. Widespread or internal disease is treated with systemic chemotherapy (doxorubicin, paclitaxel, or IFN-α).

MYCOSIS FUNGOIDES (CUTANEOUS T-CELL LYMPHOMA)

Not a fungus but a slow, progressive neoplastic proliferation of T cells. The disease is chronic and more common in men.

History/Pe

Early lesions are nonspecific, psoriatic-appearing plaques or patches that are often pruritic with a predilection for the trunk and buttocks. Later lesions are characterized by skin tumors with palpable lymph nodes (see Figure 2.2-40).

- Patients may have dermatopathic lymphadenopathy without tumor involvement of the node. However, the **internal organs can be involved,** including the lymph nodes, liver, and spleen.
- **Sézary syndrome** is the leukemic phase of cutaneous T-cell lymphoma, characterized by circulating Sézary cells in the peripheral blood, erythroderma, and lymphadenopathy.

Diagnosis

- Diagnosed by clinical features and histology, with immunologic characterization and electron microscopy showing the typical **Sézary or Lutzner cells (cerebriform lymphocytes).**
- Early lesions are clinically indistinguishable from dermatitis, **so histologic diagnosis is indicated for any dermatitis that is chronic and resistant to treatment.**

Treatment

Phototherapy is the mainstay of treatment for many patients. Early localized disease is amenable to total skin electron beam irradiation. For more extensive or advanced disease, radiation therapy is an effective option. Treatment modalities, including steroids, chemotherapy, retinoids, monoclonal antibodies, and IFN, are often combined.



FIGURE 2.2-40. Mycosis fungoides. Massive nodular infiltration of the face leads to a leonine facies. (Reproduced with permission from Wolff Ket al. Fitzpatrick's Dermatology in General Medicine, 7th ed. New York, NY: McGraw-Hill; 2008.)

CHERRY ANGIOMAS (HEMANGIOMAS)

Small, vascular, red papules that can appear anywhere on the body (see Figure 2.2-41). It is the most common **benign** vascular tumor, and it often appears with age. No treatment necessary, but can be excised for cosmetic reasons.



FIGURE 2.2-41. Cherry hemangioma. (Used with permission from Dr. Richard Usatine.)

NOTES

HIGH-YIELD FACTS IN

ENDOCRINOLOGY

Disorders of Glucose Metabolism 84
- Type 1 diabetes Mellitus 84
- Type 2 diabetes Mellitus 84
- Metabolic Syndrome 88

Thyroid Disorders 89
- Testing of Thyroid Function 89
- Hyperthyroidism/Thyrotoxicosis 89
- Hypothyroidism 93
- Thyroiditis 94
- Thyroid Neoplasms 94

Bone and Mineral Disorders 95
- osteoporosis 96
- Paget disease 97
- Hyperparathyroidism 99

Pituitary and Hypothalamic Disorders 100
- Hypopituitarism 100
- cushing Syndrome 101
- Acromegaly 101
- Hyperprolactinemia 103
- diabetes Insipidus 104
- SIAdH 105

Adrenal Gland Disorders 106
- Adrenal Insufficiency 106
- Pheochromocytoma 107
- Hyperaldosteronism 107
- congenital Adrenal Hyperplasia 108

Multiple Endocrine Neoplasias 109

Disorders of Glucose Metabolism

TYPE 1 DIABETES MELLITUS

Due to autoimmune **pancreatic β-cell destruction, leading to insulin deficiency** and abnormal glucose metabolism.

History/Pe

- Classically presents with **polyuria, polydipsia,** polyphagia, and rapid, unexplained weight loss. Patients may also present with **ketoacidosis** (see Table 2.3-2).
- Usually affects nonobese children or young adults.
- Associated with HLA-DR3 and -DR4.
- Type I DM diagnosed as an adult is known as latent autoimmune diabetes of adults (LADA).

KEY FACT

Microalbuminuria cannot be detected on routine UA protein dipstick. Instead, do a spot urine albumin-to-creatinine ratio (microalbuminuria = 30–300 mg albumin/g creatinine).

Diagnosis

- At disease onset, **anti–islet cell, anti–glutamic acid decarboxylase (anti-GAD) antibodies, anti-insulin or anti-Zn transporter antibodies** may be present in serum.
- At least one of the following is required to make the diagnosis:
  - A random plasma glucose level ≥ 200 mg/dL plus symptoms.
  - A fasting (> 8-hour) plasma glucose level ≥ 126 mg/dL. A 2-hour postprandial glucose level ≥ 200 mg/dL following an oral glucose tolerance test. (Requires repeat testing to confirm unless unequivocal hyperglycemia.)
  - Hemoglobin A_{1c} > 6.5%. (Requires repeat testing to confirm unless unequivocal hyperglycemia.)

KEY FACT

DKA and HHS often present with **paradoxic hyperkalemia.** Serum potassium may be elevated, but **total body potassium** stores are depleted (acidosis causes extracellular shift of potassium).

Treatment

- Insulin injections (see Table 2.3-1 and Figure 2.3-1) to maintain blood glucose in the normal range (80–130 mg/dL preprandial levels, < 180 mg/dL postprandial levels). **Encourage routine hemoglobin A_{1c} testing every 3 months.** Goal hemoglobin A_{1c} < 7% (< 7.5% in children). Higher blood glucose and **hemoglobin A_{1c}** levels can be tolerated, particularly in the very young and the very old, or those with multiple medical problems in light of the ↑ risk of hypoglycemia.
- Consider the use of an insulin pump, which provides a continuous, short-acting insulin infusion.
- Table 2.3-1 outlines general health maintenance guidelines.

KEY FACT

Use **NS** for initial fluid resuscitation in DKA and HHS. **Add 5% dextrose** to fluids once glucose is < 250 mg/dL.

Complications

Tables 2.3-2 and 2.3-3 outline the acute and chronic complications of DM.

TYPE 2 DIABETES MELLITUS

A dysfunction in glucose metabolism due to varying degrees of **insulin resistance in peripheral tissues** combined with **insufficient insulin secretion.**

History/Pe

- Patients may present with symptoms of hyperglycemia (polyuria, polydipsia, polyphagia, blurred vision, fatigue).
- Onset is more **insidious** than that of type 1 DM, and patients often present with complications.

TABLE 2.3-1. Treatment of Type 2 DM

Treatment	Description		
Lifestyle Modifications			
Diet	Personalized diet to encourage weight loss; avoid saturated fats and added sugars.		
Exercise	Moderate-intensity exercise for 30 minutes 5 days per week.		
Pharmacotherapy (Monotherapy or combination therapy if poor glycemic control)			
Drug	**Mechanism**	**Side effects**	**Contraindications**
Metformin	Inhibits hepatic gluconeogenesis and ↑ peripheral sensitivity to insulin.	Weight loss, GI upset, and rarely, lactic acidosis.	Contraindicated in the elderly (> 80 years of age) and in **renal insufficiency,** hepatic failure, or heart failure.
Sulfonylureas (glipizide, glyburide, glimepiride)	↑ endogenous insulin secretion.	**Hypoglycemia** and **weight gain.**	
Thiazolidinediones (rosiglitazone, pioglitazone)[a]	↑ insulin sensitivity.	Weight gain, **edema,** hepatotoxicity, and bone loss.	**Contraindicated in patients with heart failure.**
α-glucosidase inhibitors	↓ intestinal absorption of carbohydrates.	Flatulence and hypoglycemia.	
DPP-4 inhibitors (sitag**liptin,** linag**liptin,** and other **-liptins**)	Inhibit the degradation of GLP-1.	**Weight neutral.**	
Incretins (exena**tide,** liraglu**tide,** and other **-tides**)	GLP-1 agonists. Delay absorption of food; ↑ insulin secretion and ↓ glucagon secretion.	Injected subcutaneously (weekly exenatide now available). Nausea and, rarely, pancreatitis. Can cause **weight loss.**	
SGLT2 inhibitors (dapagli**flozin** and other **-flozins**)	Inhibit SGLT2 in proximal tubule to ↓ glucose reabsorption.	**UTIs,** vulvovaginal candidiasis. Can cause **weight loss** and ↓ blood pressure.	
Insulin	Given alone or in conjunction with oral agents. Types of insulin include regular, short-acting (lispro, aspart, glulisine), NPH, long acting (detemir, glargine), and combination preparations (longer + shorter acting agents like 70 NPH/30 regular).	Weight gain and hypoglycemia.	

(continues)

TABLE 2.3-1. Treatment of Type 2 DM (continued)

	General Health Maintenance
Cardiovascular risk modific tion	The presence of diabetes is equivalent to the highest risk for cardiovascular disease regardless of all other risk factors. **All diabetic patients** should be placed on a statin **regardless of lipid levels** (provided they are > 40 years old and have at least 1 other cardiovascular risk factor). Use the AHA risk calculator to determine whether **moderate** or **high-intensity** statin is recommended.[b]
BP management	Strict BP control to < 140/80 mm Hg; ACEIs/ARBs are firs -line agents.
Screening exams	Annual physical examination to screen for cardiovascular disease (BP and lipid monitoring), nephropathy (test for microalbuminuria), retinopathy (dilated-eye exams), and neuropathy (foot care evaluations).
Other	All diabetic patients > 19 years should receive the pneumonia vaccine.

[a]In September 2010, the US Food and Drug Administration restricted access to rosiglitazone because of concern for ↑ cardiovascular risks. The drug is still available but is restricted to patients currently on the medication who acknowledge that they understand the risks and to patients who cannot achieve adequate glycemic control with other medications.

[b]https://my.americanheart.org/professional/StatementsGuidelines/Prevention-Guidelines_UCM_457698_SubHomePage.jsp

- **Nonketotic hyperosmolar hyperglycemia** may be seen in the setting of poor glycemic control (see Table 2.3-2).
- Usually occurs in older adults with obesity (often abdominal) and has a strong genetic predisposition; diagnosed increasingly in obese children.
- Risk factors include obesity, rapid weight gain, a ⊕ family history, a sedentary lifestyle, increasing age, and other components of metabolic syndrome (see below).

Diagnosis

- Diagnostic criteria are the **same as those for type 1 DM.**
- Anti–islet cell and anti-GAD antibodies will be ⊖.

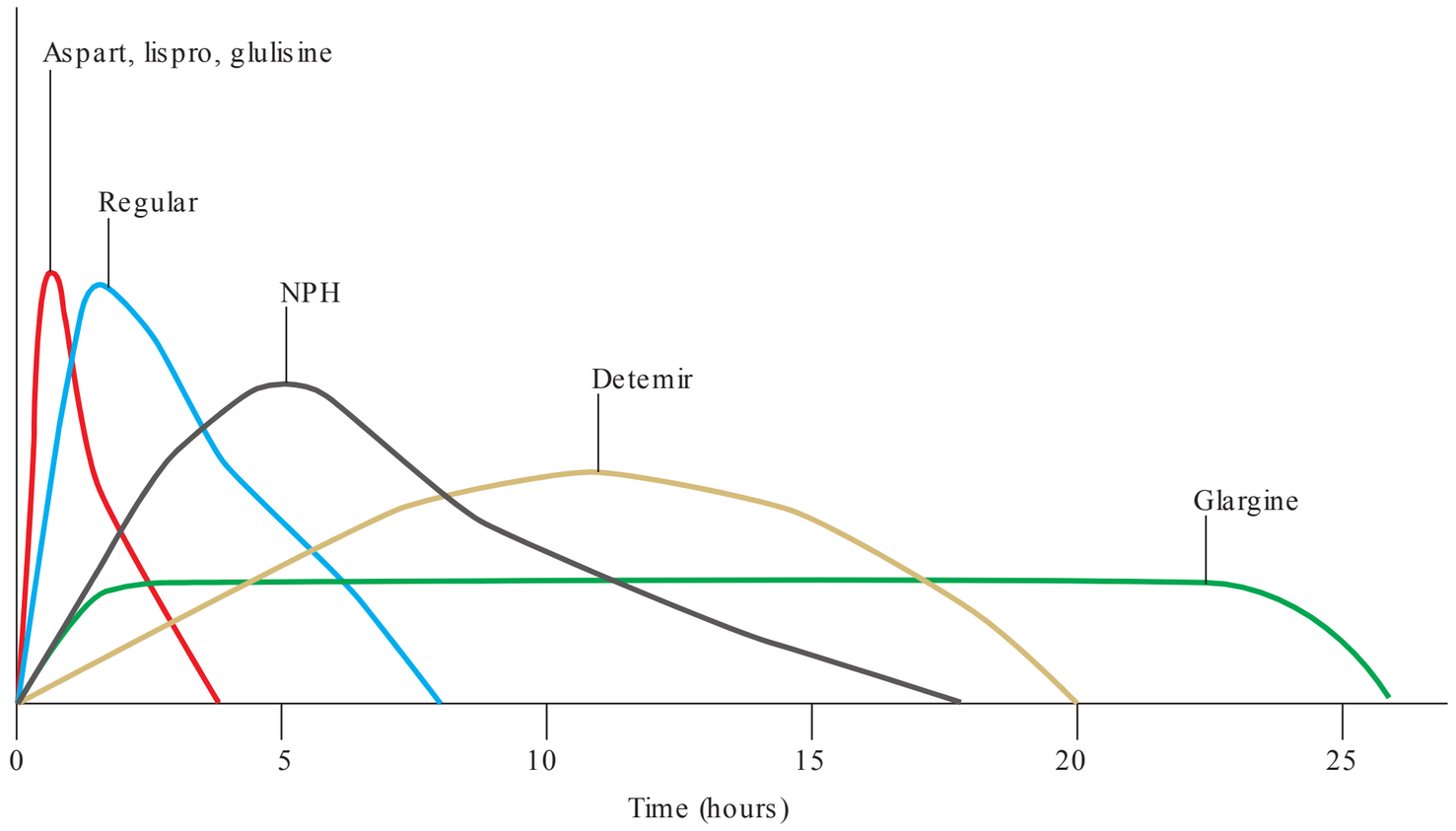


FIGURE 2.3-1. Pharmacokinetics of insulin preparations. Short acting (aspart, lispro, glulisine): onset in 5–20 minutes, peak in 0.5–3 hours, duration 3–8 hours. Regular: onset in 30 minutes, peak in 2–4 hours, duration 5–8 hours. NPH: onset in 2–4 hours, peak in 6–10 hours, duration 18–28 hours. Long acting (detemir, glargine): onset in 2 hours, peak none, duration 20–24 hours.

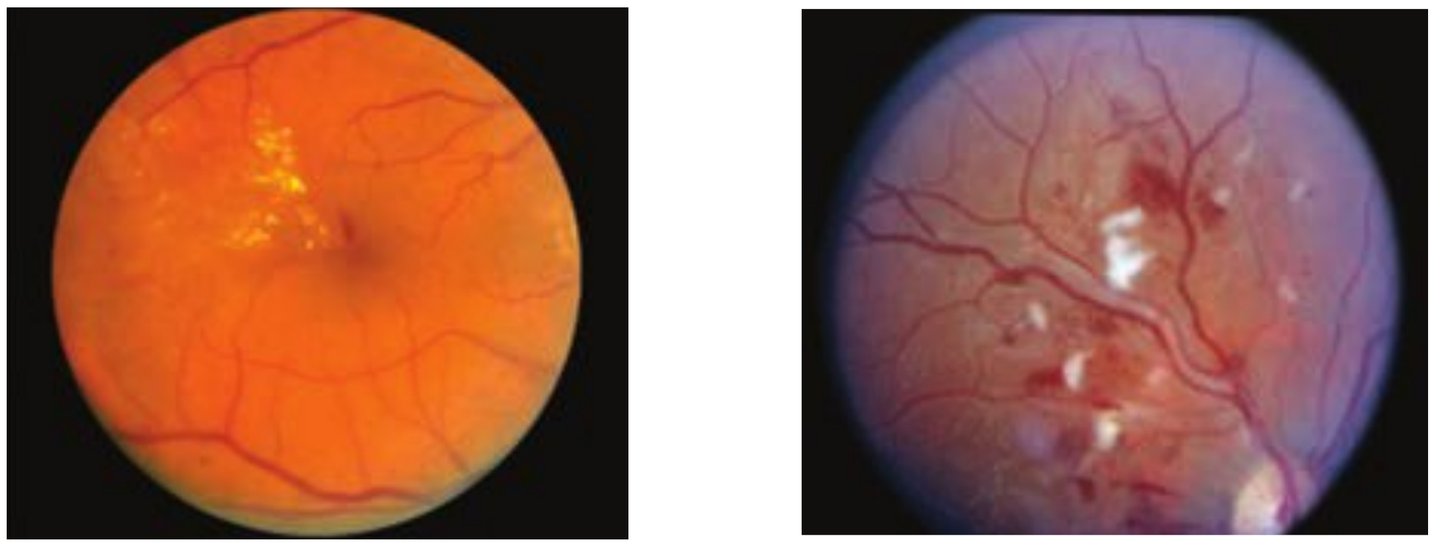
TABLE 2.3-2. Acute Complications of DM: Comparing DKA and HHS

	DKA	HHS
Patient characteristics	**Type 1 > type 2 diabetics**	**Type 2 diabetics**
Precipitants	Stress (including infections, MI, trauma, or alcohol) or noncompliance with insulin therapy.	Same. Also **dietary indiscretion.**
Symptoms	**Abdominal pain,** nausea, **vomiting, Kussmaul respirations,** mental status changes, and a **fruity, acetone breath odor.**	Profound dehydration, **mental status changes** (more prominent in HHS than DKA).
Lab values	Glucose > 250 mg/dL **Metabolic acidosis** (bicarbonate < 18 mEq/L). **↑ urine and serum ketones.** **↑ anion gap.** Serum osmolality **normal.**	Glucose > **600 mg/dL** **No acidosis** (bicarbonate > 18 mEq/L). No ketones. **Normal anion gap.** **Serum osmolality > 320 mOsm/kg.**
Treatment	Fluids, potassium, continuous **insulin (caution: will lower potassium),** phosphorus. Bicarbonate rarely used (only if pH is < 6.9). Treat initiating event. Monitor response to treatment by **closure of the anion gap.**	**Aggressive fluid ,** electrolyte replacement, and insulin. Treat the initiating event.

- **Screening recommendations:**
  - **Consider screening all patients with risk factors for diabetes (hypertension, obesity, family history, racial/ethnic minorities).**
  - **Patients with no risk factors:** Test hemoglobin A_{1c} at age 45; retest every 3 years if hemoglobin A_{1c} is < 5.7% and no other risk factors develop.

TABLE 2.3-3. Chronic Complications of DM

Complication	Description
Retinopathy (nonproliferative, proliferative)	Appears when diabetes has been present for **at least 3–5 years** (see Figure 2.3-2). Preventive measures include control of hyperglycemia and hypertension, annual eye exams, and **laser photocoagulation therapy for retinal neovascularization.**
Diabetic nephropathy	Characterized by **glomerular hyperfiltration** followed by **microalbuminuria.** Seen in patients with diabetes for > **10 years.** Preventive measures include **ACEIs** or ARBs and BP/glucose control. Kimmelstiel-Wilson nodules seen on kidney biopsy.
Neuropathy	Peripheral nerves: **Most common neuropathy.** Symmetric sensorimotor polyneuropathy leading to burning pain, foot trauma, infections, and **ulcers.** Treat with preventive **foot care** and **analgesics (amitriptyline, gabapentin, NSAIDs).** GI: **Gastroparesis** with **delayed gastric emptying.** Treat with **metoclopramide** or erythromycin. Can also get esophageal dysmotility, diarrhea/constipation. GU: **Neurogenic bladder** with decreased sensation to void, **overflow incontinence,** high postvoid residuals. Can also have **erectile dysfunction.** Cardiovascular: Orthostatic hypotension.
Macrovascular complications	Cardiovascular, cerebrovascular, and peripheral vascular disease. **Cardiovascular disease is the most common cause of death in diabetic patients.** See Table 2.3-1 for risk modification guidelines.



A B

FIGURE 2.3-2. Diabetic retinopathy. (A) Nonproliferative retinopathy presents with exudates, dot-blot hemorrhages, and microaneurysms. **(B) Proliferative retinopathy** presents with macular edema, vitreous traction, and neovascularization of the retinal vasculature. (Reproduced with permission from USMLE-Rx.com.)

- **Patients with impaired fasting glucose (> 100 mg/dL but < 126 mg/dL) or impaired glucose tolerance:** Follow up with frequent retesting.

Treatment

See Table 2.3-1 for treatment options. Treat to goal hemoglobin A_{1c} level < 7% (corresponds to an average glucose of 154 mg/dL) with more liberal goals in the elderly who are at risk of hypoglycemia.

Complications

See Tables 2.3-2 and 2.3-3 for an outline of the complications of DM.

METABOLIC SYNDROME

Also known as insulin resistance syndrome or syndrome X. Associated with an ↑ risk of CAD and mortality from a cardiovascular event.

History/Pe

Presents with abdominal obesity, high BP, impaired glycemic control, and dyslipidemia.

Diagnosis

Three out of five of the following criteria must be met:

- Abdominal obesity (↑ waist girth): ≥ 40 inches (102 cm) in men and ≥ 35 inches (88 cm) in women.
- Triglycerides ≥ 150 mg/dL.
- HDL < 40 mg/dL in men and < 50 mg/dL in women.
- BP ≥ 130/85 mm Hg or a requirement for antihypertensive drugs.
- Fasting glucose ≥ 100 mg/dL.

Treatment

Intensive weight loss, aggressive cholesterol management, and BP control. Metformin and lifestyle modifications have been shown to slow the onset of diabetes in this high-risk population.

MNEMONIC

Criteria for metabolic syndrome—

WEIGHHT

Waist **E**xpanded
Impaired **G**lucose
Hypertension
HDL↓
Triglycerides ↑

Thyroid Disorders

See Figure 2.3-3 for an overview of thyroid hormone synthesis and Figure 2.3-4 for a review of the hypothalamic-pituitary-thyroid axis.

TESTING OF THYROID FUNCTION

Thyroid function tests (TFTs) include the following (see also Table 2.3-4):

- **TSH measurement:** The single **best test for the screening of thyroid disease and for the assessment of thyroid function,** unless there is a history of brain injury (eg, tumor, radiation, trauma), in which case free T_4 should also be checked.
- **Radioactive iodine uptake (RAI) and scan:** Shows the level and distribution of iodine uptake by the thyroid. Determines if a nodule is functioning in the case of hyperthyroidism, or nonfunctioning and requires a biopsy for malignancy workup. See Table 2.3-5.
- **Total T_4 measurement:** Not an adequate screening test. Ninety-nine percent of circulating T_4 is bound to thyroxine-binding globulin (TBG). Total T_4 levels can be altered by changes in levels of binding proteins.
- **Free T_4 measurement:** The **preferred screening test for thyroid hormone levels.**

KEY FACT

↑ TBG can be found in pregnancy, estrogen administration, and infection. You do not need to treat.

KEY FACT

Exophthalmos, pretibial myxedema, and thyroid bruits are specific for Graves disease.

HYPERTHYROIDISM/THYROTOXICOSIS

Hyperthyroidism is a state of ↑ **synthesis** of T_3/T_4; thyrotoxicosis is a state of ↑ **levels** of T_3/T_4. Most commonly due to **Graves disease,** but can also result from other causes (see Table 2.3-4).

- **Graves disease:** The **autoimmune** form of hyperthyroidism. **Thyroid-stimulating antibodies** ↑ synthesis of T_3/T_4.

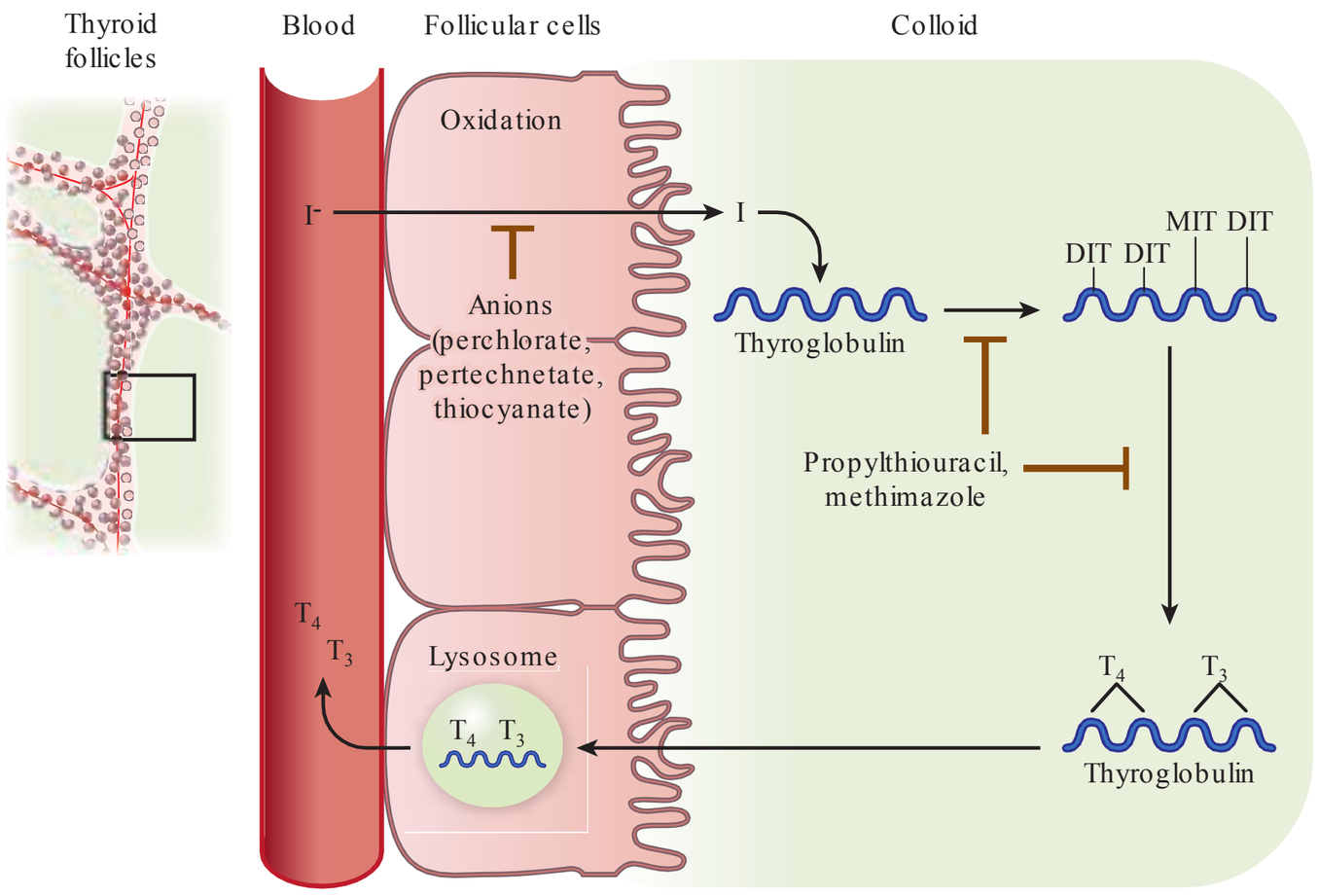


FIGURE 2.3-3. Overview of thyroid synthesis and mechanism of antithyroid medications. Iodide (I^-) is taken up from the bloodstream by follicular thyroid cells, transported to the colloid of the follicle, and oxidized to iodine (I). I combines with thyroglobulin to form monoiodotyrosine (MIT) and diiodotyrosine (DIT). Two DIT molecules combine to form T_4; MIT and DIT combine to form T_3. Iodinated thyroglobulin is transported back to the follicular cells and is cleaved in lysosomes; T_4 and T_3 are then released into the circulation.

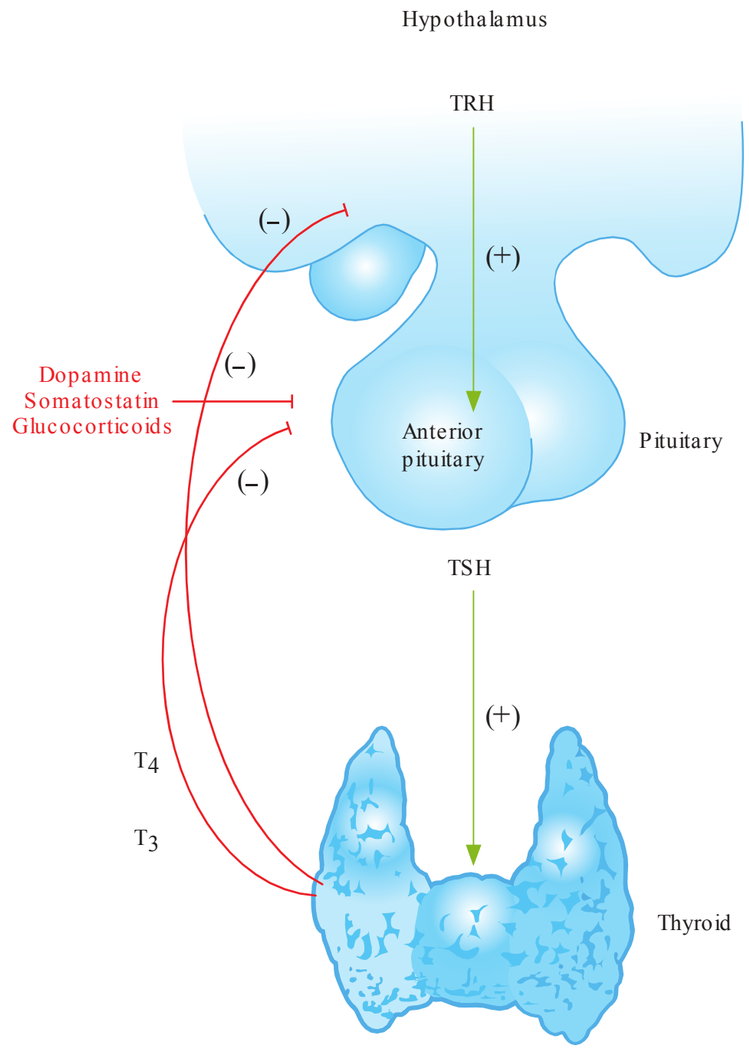


FIGURE 2.3-4. The hypothalamic-pituitary-thyroid axis. (Reproduced with permission from Molina PE. Endocrine Physiology, 3rd ed. New York, NY: McGraw-Hill; 2009.)

KEY FACT

TSH receptor-stimulating antibodies are found in patients with Graves disease.

- **Toxic adenoma/toxic multinodular goiter:** Result in hyperthyroidism due to autonomous hyperactive thyroid nodules.
- **Thyroiditis:** Due to transient inflammation of the thyroid gland with release of previously synthesized thyroid hormone; causes a temporary ↑ in circulating T_3/T_4. A hypothyroid phase may follow the hyperthyroid phase with eventual return to normal in many.
- **Fetal thyrotoxicosis:** Classically in an infant born to a mother with Graves. TSH-stimulating antibodies are IgG and can cross the placenta.

TABLE 2.3-4. TFTs in Thyroid Disease

Diagnosis	TSH	T_4	T_3	Causes
1° hyperthyroidism	↓	↑	↑	Graves disease, toxic multinodular goiter, toxic adenoma, amiodarone, postpartum thyrotoxicosis, postviral thyroiditis.
2° hyperthyroidism	Nl/↑	↑	↑	Rare. Caused by TSH-producing pituitary adenoma. TSH often inappropriately **normal** (not suppressed).
1° hypothyroidism	↑	↓	↓	Hashimoto thyroiditis, iatrogenic (radioactive ablation, excision), drugs (lithium, amiodarone).
2° hypothyroidism	↓	↓	↓	Often due to pituitary nonfunctioning macroadenomas, infiltrative diseases, or post pituitary surgery.
Subclinical hypothyroidism	↑	Nl	Nl	Often with mild elevations in TSH, asymptomatic.
Euthyroid sick syndrome	Nl	N/↓	↓	Caused by any serious illness. Will have ↑ **reverse T_3 (nonfunctional),** as T_4 is converted to rT_3 instead of T_3. Thought to be due to caloric deprivation and increased cytokines. May have transient ↑ in TSH during recovery period.

TABLE 2.3-5. Radioactive Iodine Findings in Hyperthyroidism

Diagnosis	RAI % Uptake	RAI Scan Findings	Thyroglobulin
Graves	↑	Diffuse uptak	N/A
Multinodular goiter	Nl/↑	Multiple nodules of increased uptake	N/A
Toxic adenoma	Nl/↑	One area of increased uptake	N/A
Thyroiditis, iodine exposure, extraglandular production	↓	Low uptake	↑
Exogenous thyroid hormone	↓	Low uptake	↓

History/PE

- Presents with **weight loss, heat intolerance, anxiety, palpitations, ↑ bowel frequency, myopathy/proximal muscle weakness,** insomnia, and menstrual abnormalities.
- Examination reveals warm, moist skin, goiter, sinus **tachycardia,** or **atrial fibrillation (AF),** fine **tremor, lid lag,** and hyperactive reflexes. **Exophthalmos (direct stimulation of orbital fibroblasts by antibodies),** pretibial myxedema, and thyroid bruits are seen only in Graves disease (see Figure 2.3-5).

Diagnosis

The initial test of choice is a serum TSH level, followed by T_4 levels and, rarely, T_3 (unless TSH is low and free T_4 is not elevated). May need additional information provided by RAI scans (see Figure 2.3-6) and thyroglobulin levels. See Tables 2.3-4 and 2.3-5.

Treatment

- **Symptomatic treatment: Propranolol (or metoprolol, atenolol)** to manage adrenergic symptoms.
- **Pharmacologic treatment:** Antithyroid drugs (methimazole or propylthiouracil).
- **Definitive treatment:** Radioactive ^{131}I thyroid ablation or total thyroidectomy (less common in the United States).
- Administer levothyroxine (oral T_4 replacement) to prevent hypothyroidism in patients who have undergone ablation or surgery.
- Administer steroids to treat severe ophthalmopathy (if causing diplopia or threatening vision).
- See Table 2.3-6 for adverse drug reactions associated with antithyroid treatments.

Complications

Thyroid storm: An acute, life-threatening form of thyrotoxicosis. Treat urgently with antithyroid drugs, IV esmolol, and corticosteroids. High-dose

KEY FACT

Thyroid storm is an acute, life-threatening form of thyrotoxicosis that may present with AF, fever, and delirium. Administer antithyroid drugs, then iodine, IV esmolol, and steroids and admit to the ICU.

Q 1

A 24-year-old woman with hypothyroidism presents at 10 weeks' gestation for a prenatal visit. Her only medication is levothyroxine. What adjustment is probably needed to her levothyroxine dose?

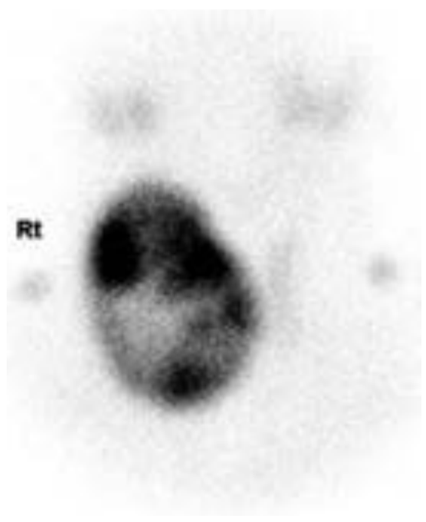
Q 2

A 10-year-old boy presents to the ED with 2 weeks of polyuria and polydipsia together with new-onset lethargy. Physical examination reveals signs of severe dehydration, and labs reveal a blood glucose level of 500 mg/dL. The diagnosis of DKA is made, and the patient is started on insulin and IV fluids. His glucose on recheck is 250 mg/dL. What is the next best step in management?

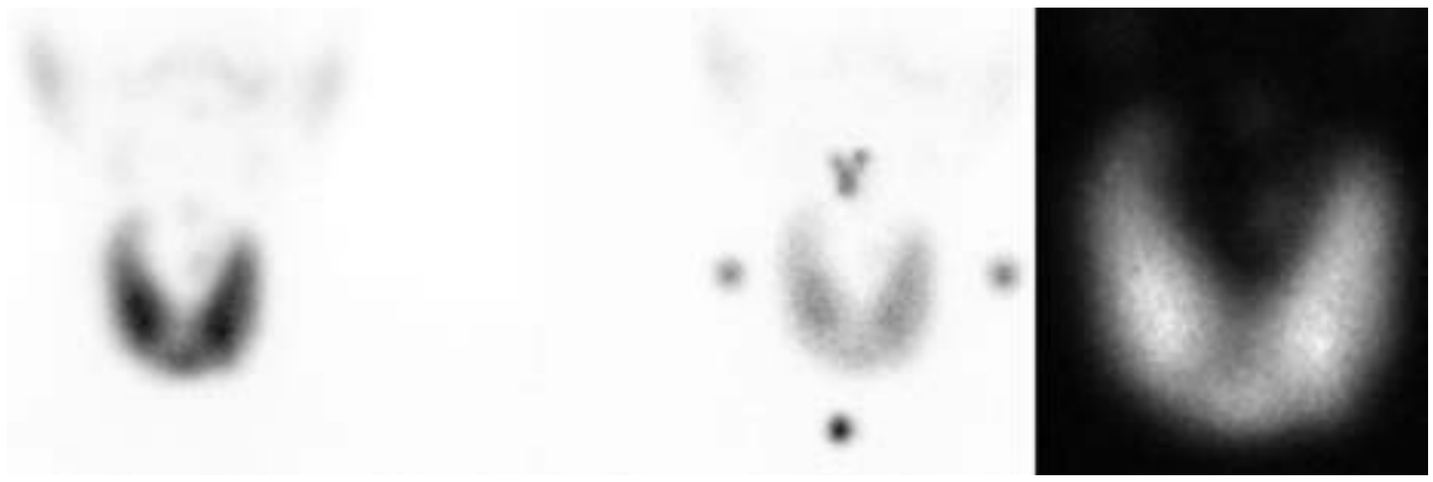


A B

FIGURE 2.3-5. Physical signs of Graves disease. (A) Graves ophthalmopathy. **(B)** Pretibial myxedema. (Reproduced with permission from USMLE-Rx.com.)



A



B

FIGURE 2.3-6. Radioactive iodine uptake scans. 99m-Technetium pertechnetate thyroid scans showing **(A)** multinodular areas of increased uptake and **(B)** diffuse uptake as seen in Graves disease. (Part A reproduced with permission from Cho EA et al. A case of masked toxic adenoma in a patient with non-thyroidal illness, BMC Endocr Disord 2014 Jan 2;14:1. Part B reproduced with permission from Coutinho E et al. Graves' disease presenting as pseudotumor cerebri: a case report, J Med Case Rep 2011 Feb 15;5:68.)

1 **A**

Her dose will probably have to be ↑ (sometimes by up to 50%!). Increased TBG levels in pregnancy lead to ↓ free T_3/T_4 levels and ↑ TSH.

2 **A**

Add 5% dextrose to the IV fluids. In the management of DKA, it is important to start IV fluids and insulin immediately. Initially, the goal is to rehydrate the patient and lower blood glucose, but as blood glucose reaches 250–300 mg/dL, it is important to add 5% dextrose to ↓ the risk of hypoglycemia.

TABLE 2.3-6. Adverse Drug Reactions for Thyrotoxicosis Treatments

Drug/Treatment	Adverse Reactions
Propylthiouracil	Allergic reaction, rash, arthralgias, **agranulocytosis,** vasculitis, liver failure (black box warning). Safe to use in pregnancy.
Methimazole	Allergic reaction. **Contraindicated in pregnancy.** **Agranulocytosis.** Cholestasis.
Radioactive ^{131}I thyroid ablation	Most common side effect is hypothyroidism (most common when treating patients with Graves). **Contraindicated in pregnancy.** Will initially **worsen** ophthalmopathy.
Total thyroidectomy	Hypothyroidism, hypoparathyroidism, damage to nearby structures (recurrent laryngeal nerve).

potassium iodide (SSKI) is also effective. Untreated hyperthyroidism can also lead to long-term **bone loss.**

HYPOTHYROIDISM

A state involving ↓ levels of T_3/T_4. Most commonly due to **Hashimoto thyroiditis,** but can result from other causes (see Table 2.3-4).

- **Hashimoto thyroiditis (autoimmune hypothyroidism):** Associated with ⊕ **antithyroglobulin and antithyroid peroxidase (anti-TPO) antibodies** that precipitate thyroid destruction.
- **Thyroiditis (postpartum, postviral, subacute):** Can have a hypothyroid phase that follows the hyperthyroid phase. Hypothyroidism can be permanent.
- **Secondary hypothyroidism:** Due to pituitary tumors or pituitary surgery.
- **Congenital hypothyroidism:** Most common etiology is thyroid dysgenesis. Presents as **failure to thrive,** hypotonia, **umbilical hernias,** prolonged jaundice.
- **Generalized resistance to thyroid hormone: Rare. Elevated T_3/T_4, normal to elevated TSH.**

History/Pe

- Presents with weakness, fatigue, **cold intolerance, constipation,** weight gain, **depression,** hair loss, menstrual irregularities, myopathy, and **hoarseness.**
- Examination reveals **dry, cold, puffy skin** accompanied by edema, **bradycardia,** and delayed relaxation of deep tendon reflexes.

Diagnosis

The initial test of choice is serum TSH level, followed by free T_4 levels. See Table 2.3-4. Other lab abnormalities include **high LDL,** ↑ triglycerides, ↑ CK, hypothermia.

Treatment

For uncomplicated hypothyroidism (eg, Hashimoto disease), administer levothyroxine. In **subclinical hypothyroidism** (↑ TSH, normal T_4), treat with levothyroxine if **TSH > 10 mU/L.**

Complications

- **Increased risk of thyroid lymphoma** in patients with Hashimoto disease.
- **Myxedema coma:** Severe hypothyroidism with ↓ **mental status, hypothermia,** hypotension, bradycardia, hypoventilation. Mortality is 30–60%. Admit to the ICU and treat urgently with IV levothyroxine and IV hydrocortisone (if adrenal insufficiency has not been excluded).

THYROIDITIS

Inflammation of the thyroid gland. Common subtypes include subacute granulomatous, radiation-induced, autoimmune, postpartum, and drug-induced (eg, amiodarone) thyroiditis.

KEY FACT

Subacute thyroiditis is not a "cute" thyroiditis—it is painful!

History/Pe

- The **subacute form presents with a tender thyroid,** malaise, and URI symptoms.
- All other forms are associated with painless goiter.

Diagnosis

Thyroid dysfunction (typically thyrotoxicosis followed by hypothyroidism), with ↓ uptake on RAI and scan during the hyperthyroid phase.

Treatment

- β-blockers for hyperthyroidism; levothyroxine for hypothyroidism.
- Subacute thyroiditis is usually self-limited; for severe cases, treat with NSAIDs or with oral corticosteroids.

THYROID NEOPLASMS

Thyroid nodules are very common and show an ↑ incidence with age. Most (~ 95%) are benign.

MNEMONIC

Thyroid neoplasms—

The most Popular is Papillary

Papillae (branching)
Palpable lymph nodes
"**P**upil" nuclei ("Orphan Annie" nuclei)
Psammoma bodies within lesion (often)
Also has a **P**ositive **P**rognosis

History/Pe

- Usually asymptomatic on initial presentation; discovered incidentally with imaging for other purposes (eg, carotid ultrasound) or on examination.
- Hyperfunctioning nodules present with hyperthyroidism.
- Large nodules adjacent to the trachea/esophagus present with local symptoms (dysphagia, dyspnea, cough, choking sensation).
- An ↑ risk of malignancy is associated with a **history of childhood neck irradiation, "cold" nodules** (minimal uptake on RAI scan), female sex, age < 20 or > 70, firm and fixed solitary nodules, a ⊕ family history, and **rapidly growing nodules with hoarseness.**
- Check for anterior cervical lymphadenopathy. Carcinoma (see Table 2.3-7) may be **firm and fixed.**
- Medullary thyroid carcinoma is associated with multiple endocrine neoplasia (MEN) type 2.

KEY FACT

Check calcitonin levels if medullary cancer is suspected!

KEY FACT

Hyperfunctioning thyroid nodules are not malignant.

Diagnosis

See Figure 2.3-7 **for a diagnostic workup of thyroid nodules.**

Treatment

- **Benign fine-needle aspiration (FNA):** Follow with physical examination/ultrasonography to assess for continued nodule growth or for the development of suspicious characteristics (eg, microcalcifications, ↑ vascular flow).

TABLE 2.3-7. Types of Thyroid Carcinoma

Type[a]	Characteristics	Prognosis
Papillary	Represents **75–80% of thyroid cancers.** The female-to-male ratio is 3:1. Slow growing; found in thyroid hormone–producing follicular cells. **Lymphatic spread.**	Ninety percent of patients ≥ 10 years after diagnosis; the prognosis is worse in elderly patients or those with large tumors.
Follicular	Accounts for 17% of thyroid cancers; found in thyroid hormone–producing follicular cells. **Hematologic spread.**	Same as above.
Medullary	Responsible for 6–8% of thyroid cancers. Found in calcitonin-producing C cells; the prognosis is related to degree of vascular invasion.	Eighty percent of patients survive at least 10 years after surgery. Consider MEN 2A or 2B based on family history.
Anaplastic	Accounts for < 2% of thyroid cancers; rapidly enlarges and metastasizes.	Ten percent of patients survive for > 3 years.

[a]Tumors may contain mixed papillary and follicular pathologies.

- **Malignant FNA:** Surgical resection with hemi- or total thyroidectomy is first-line treatment; adjunctive radioiodine ablation following excision is appropriate for some follicular lesions.
- **Indeterminate FNA:** Watchful waiting vs hemithyroidectomy (10–30% chance of malignancy). If resected, await final pathology to guide further treatment.

Bone and Mineral Disorders

Figure 2.3-8 reviews calcium and phosphate regulation.

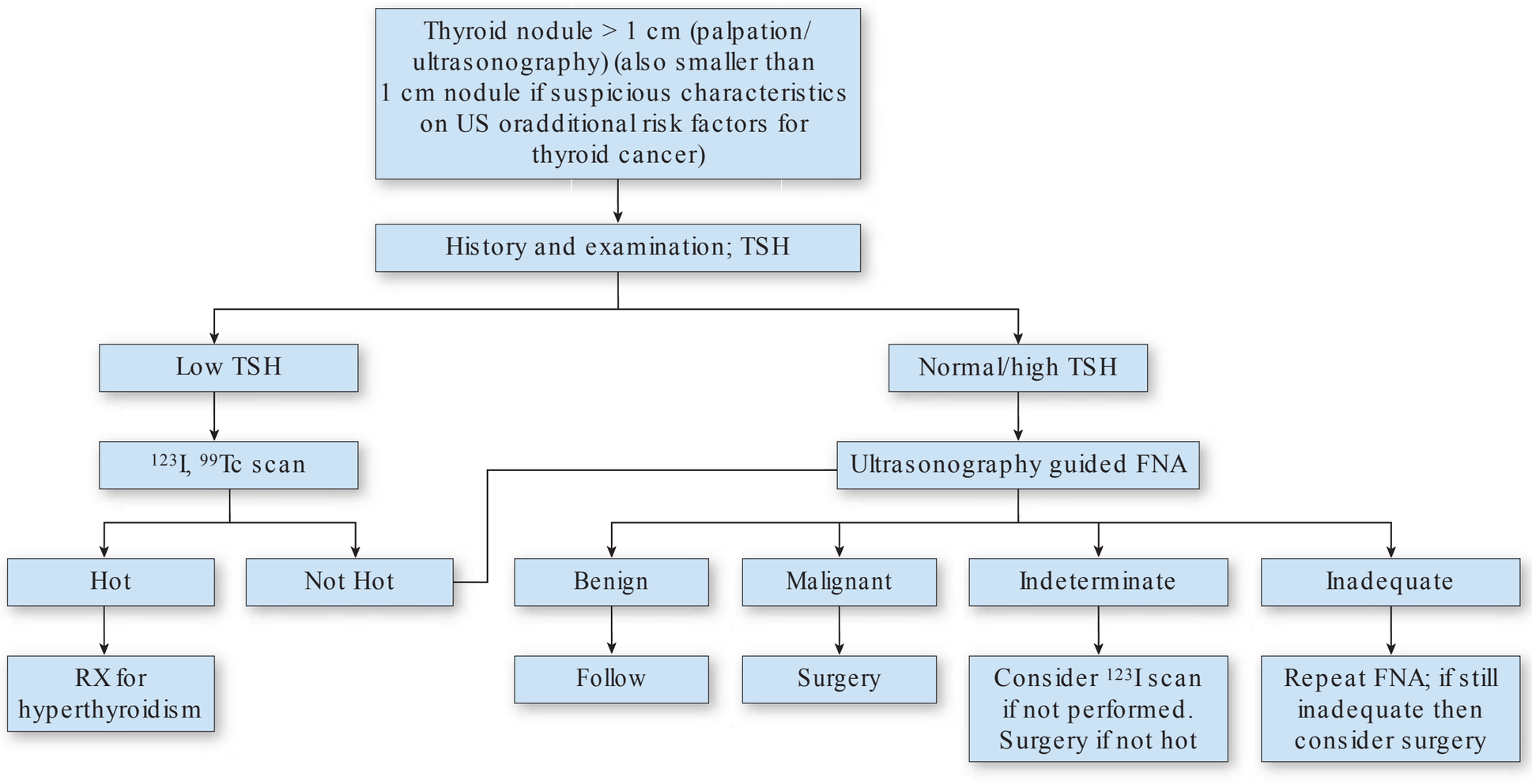


FIGURE 2.3-7. Diagnostic steps in the workup of a thyroid nodule. (Reproduced with permission from Lalwani AK. Current Diagnosis and Treatment in Otolaryngology—Head and Neck Surgery, 3rd ed. New York, NY: McGraw-Hill; 2012.)

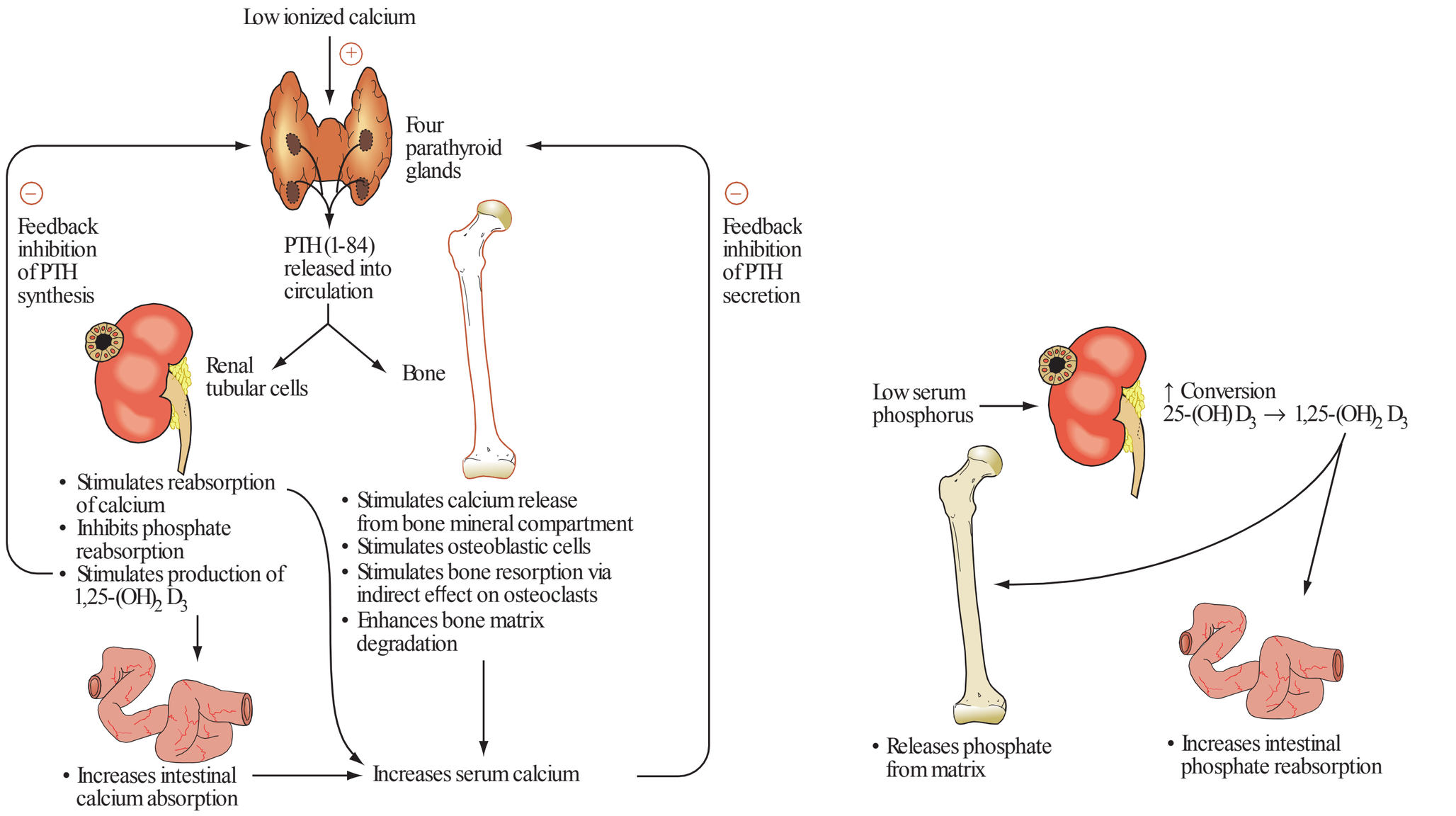


FIGURE 2.3-8. Overview of calcium and phosphate regulation. (Adapted with permission from Chandrosoma P et al. Concise Pathology, 3rd ed. Stamford, CT: Appleton &Lange; 1998.)

OSTEOPOROSIS

A common metabolic bone disease characterized by low bone mass. It most often affects thin postmenopausal women (17%), especially Caucasians and Asians, with risk doubling after age 65. Males are also at risk for osteoporosis, but the diagnosis is often overlooked.

History/Pe

- Commonly asymptomatic even in the presence of a vertebral fracture.
- Examination may reveal **hip fractures, vertebral compression fractures** (loss of height and progressive thoracic kyphosis), and/or distal radius fractures (Colles fracture) following minimal trauma (see Figure 2.3-9).
- **Smoking, age,** excessive caffeine or alcohol intake, a history of estrogen-depleting conditions in women (eg, amenorrhea, eating disorders) or hypogonadism in men, uncontrolled hyperthyroidism, chronic inflammatory disease, and **corticosteroid use** are all associated with an ↑ risk.

Diagnosis

- **Dual-energy x-ray absorptiometry (DEXA):** Recommended as screening test for all women > 65 and men > 70, and those with other risk factors for osteoporosis. Osteoporosis diagnosed when **bone mineral density (BMD) is 2.5 standard deviations (SDs)** less than seen in a young, normal person (T-score), with sites reported including the vertebral bodies, proximal femur, and distal radius. BMD between 1 and 2.5 SDs below normal is diagnostic of **osteopenia.**
- **Lab values: Normal** calcium, phosphate, parathyroid hormone levels.
- **X-ray films:** Global demineralization is apparent only after > 30% of bone density is lost.

KEY FACT

Do not confuse osteoporosis with osteomalacia. **Osteomalacia** is a mineralization defect often due to severe vitamin D deficiency that presents with bone pain, decreased calcium/phosphorus, and 2° hyperparathyroidism.

KEY FACT

Osteoporosis is the most common cause of pathologic fractures in thin, elderly women and men.

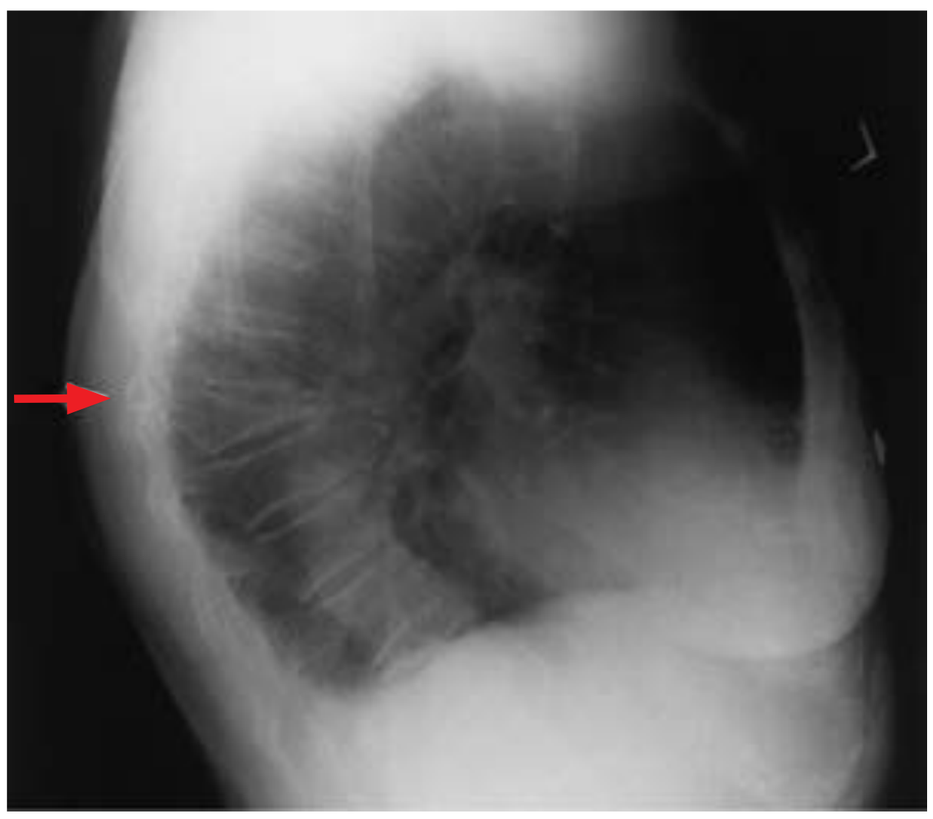


FIGURE 2.3-9. Radiographic findings in osteoporosis Lateral thoracic spine radiograph shows osteoporosis and an anterior wedge deformity of a lower thoracic vertebral body with associated kyphosis. This is a typical insufficiency fracture in osteoporotic patients. (Reproduced with permission from Fauci AS et al. Harrison's Principles of Internal Medicine, 17th ed. New York, NY: McGraw-Hill; 2008.)

Treatment

- Prevention and treatment with **calcium** and **vitamin D supplementation.**
- Smoking cessation and weight-bearing exercises help maintain and even restore some bone density.
- **Bisphosphonates** (eg, alendronate, risedronate, ibandronate, zoledronic acid) are used in the treatment of osteoporosis, **not** osteopenia.
- Other drugs include antiresorptive agents like selective estrogen receptor modulators (eg, raloxifene), intranasal calcitonin, and denosumab (a monoclonal antibody to RANK-L), as well as anabolic agents like teriparatide (analogue of parathyroid hormone, PTH).

Complications

Fracture is the most devastating consequence of low BMD/osteoporosis, carrying a **50% increase in mortality** in the year following hip fracture.

PAGET DISEASE

Characterized by an ↑ rate of bone turnover with both excessive resorption and formation of bone, leading to a **"mosaic" lamellar bone pattern** on x-ray film. Suspected to be due to the effects of a latent viral infection in genetically susceptible individuals. Occurs in roughly 4% of men and women > 40 years of age based on autopsy findings, though only a low percentage present clinically. Associated with 1° hyperparathyroidism and ↑ risk of osteosarcoma.

History/Pe

- Usually asymptomatic, but may present with aching bone or joint pain, headaches (if the skull is involved), bony deformities, fracture at a pagetoid site, or nerve entrapment (leads to loss of hearing in 30–40% of cases involving the skull).
- The disease can affect one (monostotic) or many (polyostotic) bones, with the skull, vertebral bodies, pelvis, and long bones most commonly affected.

KEY FACT

↑ serum alkaline phosphatase with normal gamma-glutamyl transpeptidase (GGT) points to **bone** etiology, **NOT a liver etiology.**

KEY FACT

Bone pain and hearing loss → think Paget disease.

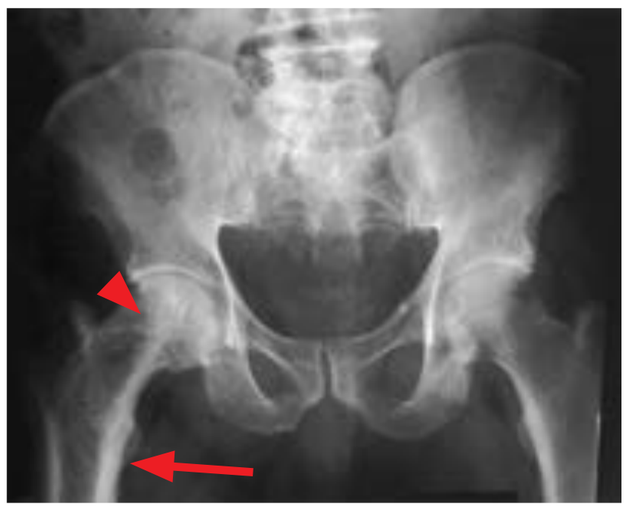


FIGURE 2.3-10. Radiographic findings in Paget disease. Pelvic radiograph demonstrates a thickened cortex (arrow), thickened trabeculae (arrowhead), and expansion of the right femoral head, classic signs of Paget disease. (Reproduced with permission from Fauci AS et al. Harrison's Principles of Internal Medicine, 17th ed. New York, NY: McGraw-Hill; 2008.)

Diagnosis

- **Radiographic diagnosis** (lytic and sclerotic lesions; see Figure 2.3-10). Diagnose via **plain films,** but baseline **radionuclide bone scan** necessary to characterize extent of disease (see Figure 2.3-11).
- **Lab values:** Abnormalities include ↑ **serum alkaline phosphatase with normal calcium and phosphate levels.** Must be distinguished from metastatic bone disease.

Treatment

- **Most patients are asymptomatic and require no treatment.**
- There is no cure for Paget disease. Treat with calcium and vitamin D supplementation. In the setting of severe pain, involvement of a vulnerable site (femoral neck), or fracture, **bisphosphonates** and calcitonin can be used to slow osteoclastic bone resorption; NSAIDs and acetaminophen can be given for pain management.

Complications

Pathologic fractures, high-output cardiac failure (from AV connections), osteosarcoma (up to 1%).

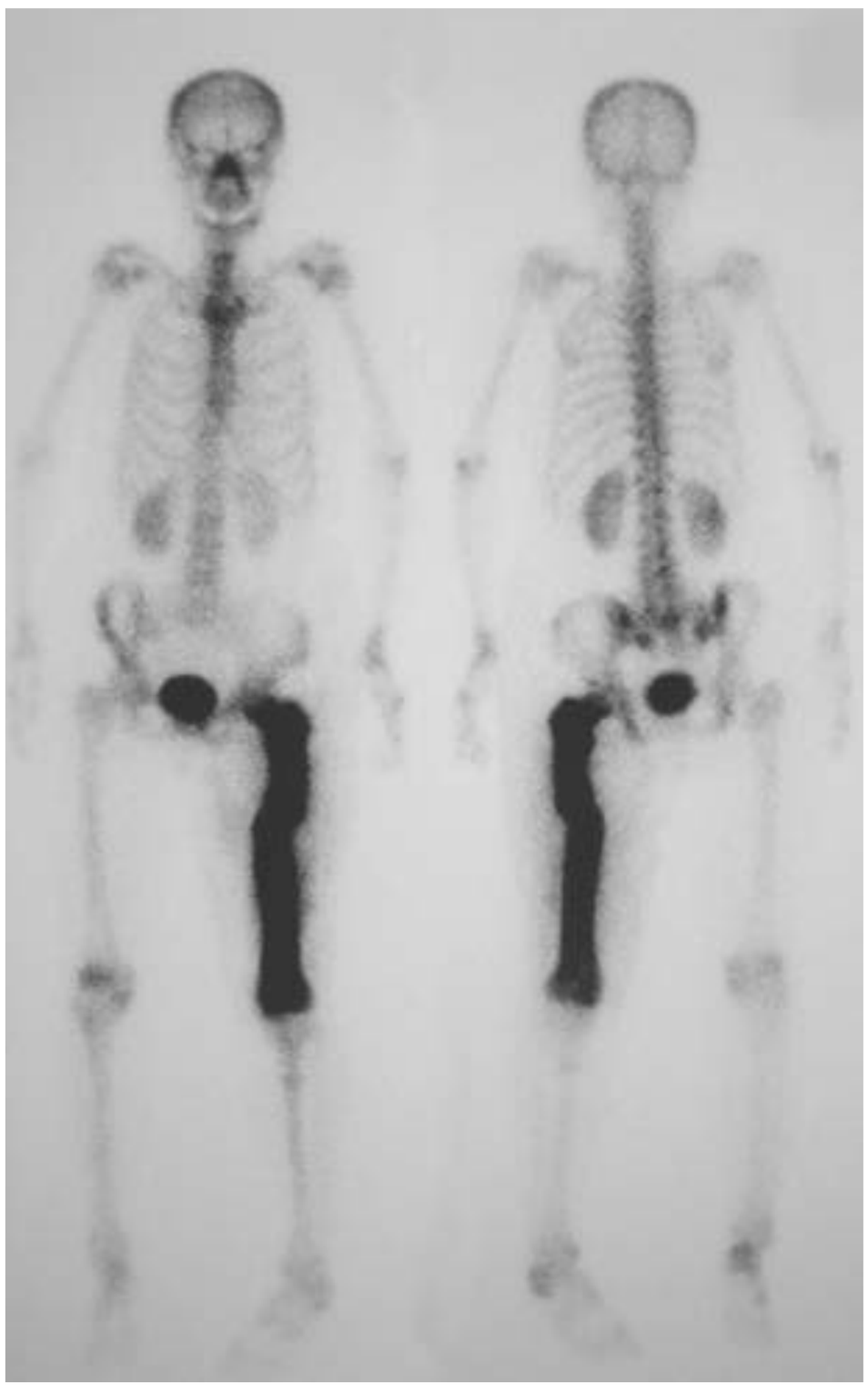


FIGURE 2.3-11. Bone scan in Paget disease. Dark areas represent increased bone-seeking isotope uptake and depicts severe disease in the left femur. (Reproduced with permission from Takigami I et al. Functional bracing for delayed union of a femur fracture associated with Paget's disease of the bone in an Asian patient: a case report, J Orthop Surg Res 2010 May 12;5:33.)

HYPERPARATHYROIDISM

See Figure 2.3-8 for the effects of PTH on serum calcium and phosphate regulation. For a more thorough review of hypo- and hypercalcemia, see the Renal/Genitourinary chapter.

- **1° hyperparathyroidism:** Most cases (80%) are due to a single hyperfunctioning adenoma, with the rest (15%) resulting from parathyroid hyperplasia and, rarely (5%), parathyroid carcinoma.
- **2° hyperparathyroidism:** A physiologic ↑ of PTH in response to **renal insufficiency (due to ↓ production of 1-25 dihydroxyvitamin D),** calcium deficiency, or vitamin D deficiency.
- **3° hyperparathyroidism:** Seen in **dialysis patients** with long-standing 2° hyperparathyroidism that leads to hyperplasia of the parathyroid glands. When one or more of the glands become autonomous, 3° hyperparathyroidism results.
- **Pseudohypoparathyroidism:** PTH resistance. Elevated PTH levels but ineffective at target organs. Hypocalcemia and hyperphosphatemia. Associated with Albright hereditary osteodystrophy (may have shortened fourth metatarsal or metacarpal bones).

History/Pe

Most cases of 1° hyperparathyroidism are **asymptomatic** but may show signs and symptoms of **hypercalcemia** (see Renal/Genitourinary chapter).

Diagnosis

- Lab results in 1° hyperparathyroidism reveal **hypercalcemia, hypophosphatemia,** and hypercalciuria. Intact PTH is inappropriately ↑ relative to total and ionized calcium (see Table 2.3-8).
- DEXA may reveal low BMD or frank osteoporosis in the distal radius or other sites.
- A ^{99m}Tc sestamibi scan, in conjunction with thyroid ultrasonography, can help localize a solitary adenoma.

Treatment

- **Parathyroidectomy** if the patient is symptomatic or if certain criteria are met (↑↑ calcium,↑ creatinine, ↓ BMD, age < 50). In the case of a solitary adenoma, 1 gland can be removed. In the setting of hyperplasia, 3.5 glands must be removed.

TABLE 2.3-8. Lab Values in Hyperparathyroidism

	PTH	CALCIUM	PO_4
1°	↑	↑	↓
2°	↑	Nl/↓	↑ (when etiology is renal failure)
3°	↑	↑	↑
Ectopic PTHrP[a]	↓	↑	Nl/↓

[a]PTH-releasing peptide (PTHrP) is a member of the PTH family and acts on the same PTH receptors. Some tumors (eg, breast, lung) produce PTHrP, causing hypercalcemia of malignancy.

KEY FACT

Hypercalcemia is associated with "stones, bones, moans, groans, and psychiatric overtones." Administer IV fluids and then loop diuretics. Add bisphosphonates if malignancy, ± calcitonin.

KEY FACT

Etiologies of **HYPO**parathyroidism include **iatrogenic (postsurgical),** autoimmune, congenital (DiGeorge), infiltrative (hemochromatosis, Wilson) diseases.

Q

An asymptomatic 36-year-old man presents for his annual physical. Routine labs reveal a serum calcium level of 11.3 mg/dL. He returns in 2 weeks, and his serum calcium level remains elevated. Additional studies show a normal serum PTH level and a low 24-hour urinary calcium level. What is the most likely diagnosis?

- For acute hypercalcemia, give **IV fluids, loop diuretics, and an IV bisphosphonate.**
- In patients with renal insufficiency, administer oral phosphate binders (calcium salts, sevelamer hydrochloride, and lanthanum carbonate) and restrict dietary phosphate intake to prevent 2° hyperparathyroidism.
- Cinacalcet is a calcimimetic that acts to lower serum PTH levels and is approved for use in hyperparathyroidism due to renal failure or in patients who cannot undergo surgery.

Complications

Hypercalcemia is the most severe complication of 1° hyperparathyroidism. Postparathyroidectomy, watch out for hungry bone syndrome (severe and prolonged **hypocalcemia** due to acute reversal of PTH and ↑ in bone uptake of calcium, phosphate, and magnesium).

Pituitary and Hypothalamic Disorders

Figure 2.3-12 illustrates the hypothalamic-pituitary axis. The sections that follow outline the manner in which the components of this axis interact with target organs in various pathologic states.

HYPOPITUITARISM

Caused by mass lesions (tumors, cysts), surgery, radiation, Sheehan (pituitary infarction, often 2/2 postpartum hemorrhage), apoplexy (hemorrhage), infiltrative disorders (hemochromatosis), infections. Gonadotropins and growth hormone often affected first.

History/Pe

See corresponding sections for presentation of pituitary hormone deficiencies. May present **suddenly** (apoplexy, Sheehan) or **gradually** (radiation, infiltrative diseases).

Diagnosis

Measure 8 AM cortisol, free T_4 (TSH not diagnostic), testosterone/estradiol levels, insulin-like growth factor 1 (IGF-1).

Treatment

Treat underlying disorder. See corresponding sections for treatments of specific hormone deficiencies.

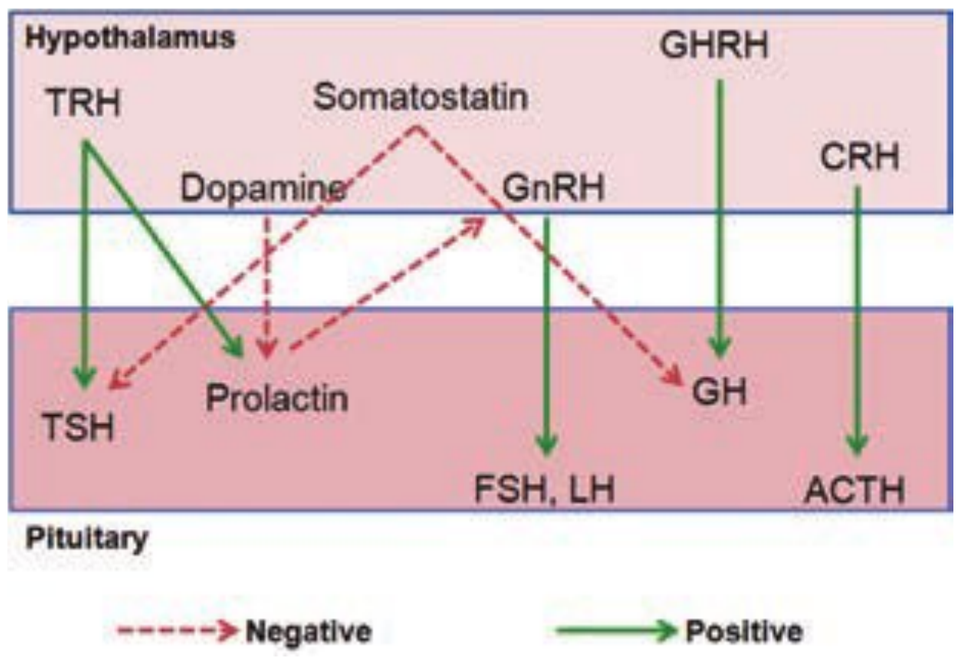


FIGURE 2.3-12. The hypothalamic-pituitary axis. (Reproduced with permission from USMLE-Rx.com.)

A

Familial hypocalciuric hypercalcemia (FHH), an inherited disorder due to mutations in a calcium-sensing receptor present in the parathyroid and kidney, presents with elevated serum calcium levels. Unlike patients with 1° hyperparathyroidism, these patients are asymptomatic and have **low urinary calcium levels. No treatment** is required.

CUSHING SYNDROME

Elevated serum cortisol levels. Cushing syndrome is most frequently from prolonged treatment with exogenous corticosteroids. The most common endogenous cause is hypersecretion of ACTH from a pituitary adenoma (known as Cushing disease; see Figure 2.3-13). Other endogenous causes include excess adrenal secretion of cortisol (eg, bilateral adrenal hyperplasia, adenoma, adrenal cancer) and ectopic ACTH production from an occult neoplasm (eg, carcinoid tumor, medullary thyroid cancer, small cell lung cancer).

History/Pe

See Figure 2.3-14 **for classic signs and symptoms of Cushing syndrome.**

Diagnosis

Diagnosis follows a stepwise progression of tests. See Figure 2.3-15 for the diagnostic algorithm. Table 2.3-9 outlines important lab findings that aid in diagnosis.

Treatment

- **Surgical resection** of the source (pituitary, adrenal, neoplasm).
- Permanent hormone replacement therapy to correct deficiencies after treatment of the 1° lesion.

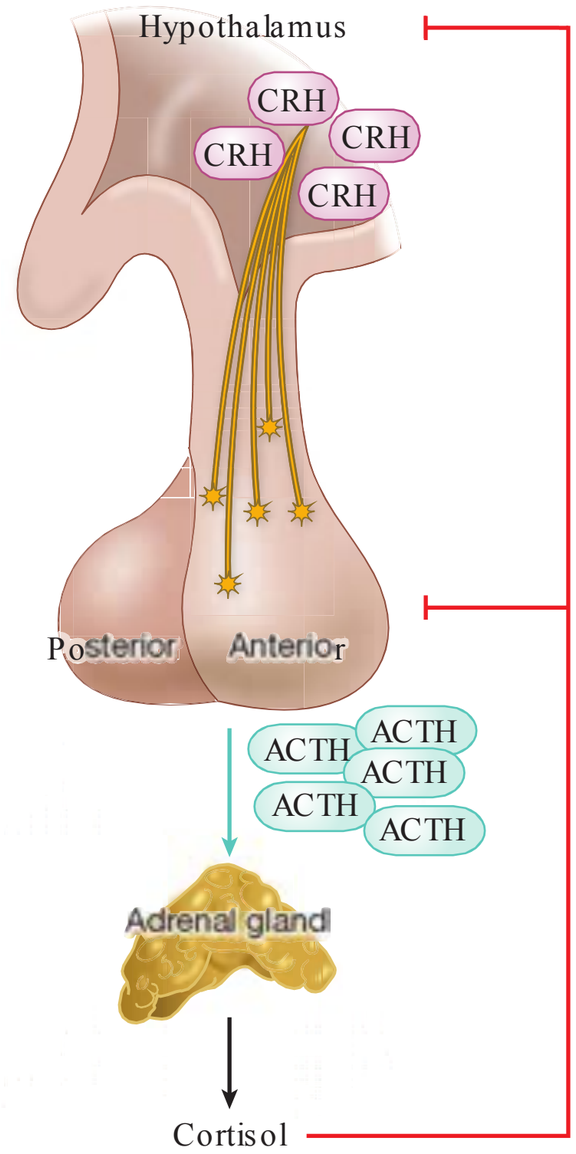


FIGURE 2.3-13. The hypothalamic-pituitary axis: Cushing disease.

ACROMEGALY

Elevated growth hormone (GH) levels in adults, most commonly due to a benign pituitary GH-secreting adenoma (see Figure 2.3-16). Children with excess GH production present with **gigantism.**

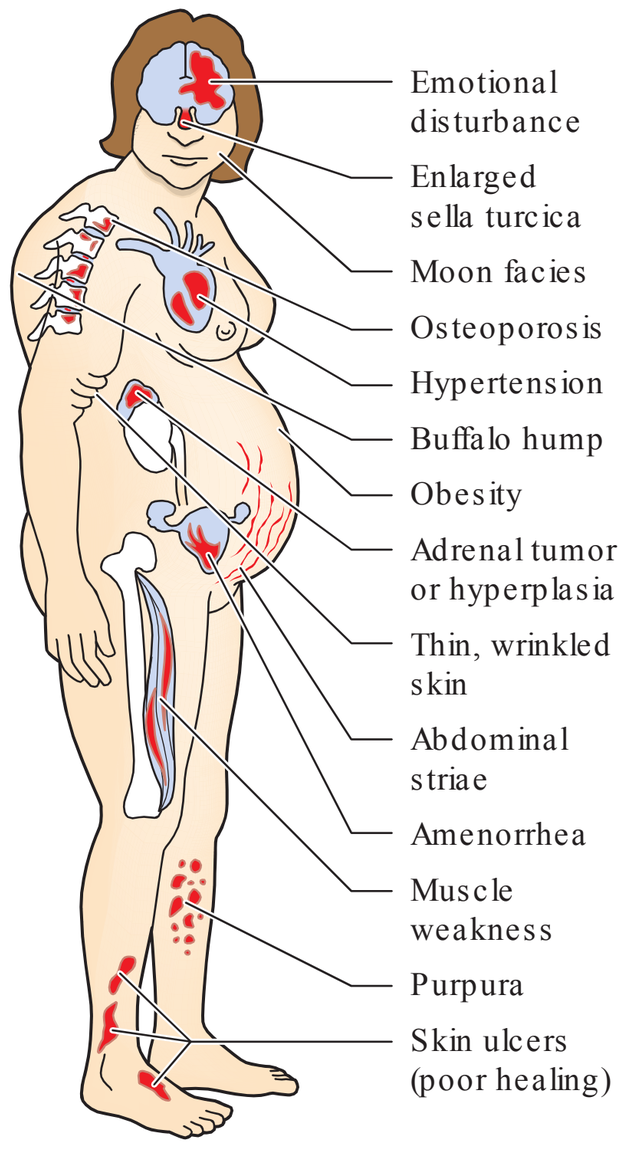


FIGURE 2.3-14. Physical findings in Cushing syndrome. (Reproduced with permission from USMLE-Rx.com.)

KEY FACT

Cushing syndrome = too much cortisol. **Cushing disease** = too much cortisol from an ACTH-producing pituitary adenoma.

KEY FACT

In Cushing disease, cortisol secretion remains elevated with the low-dose (1 mg) dexamethasone test but is suppressed with the high-dose (8 mg) dexamethasone test.

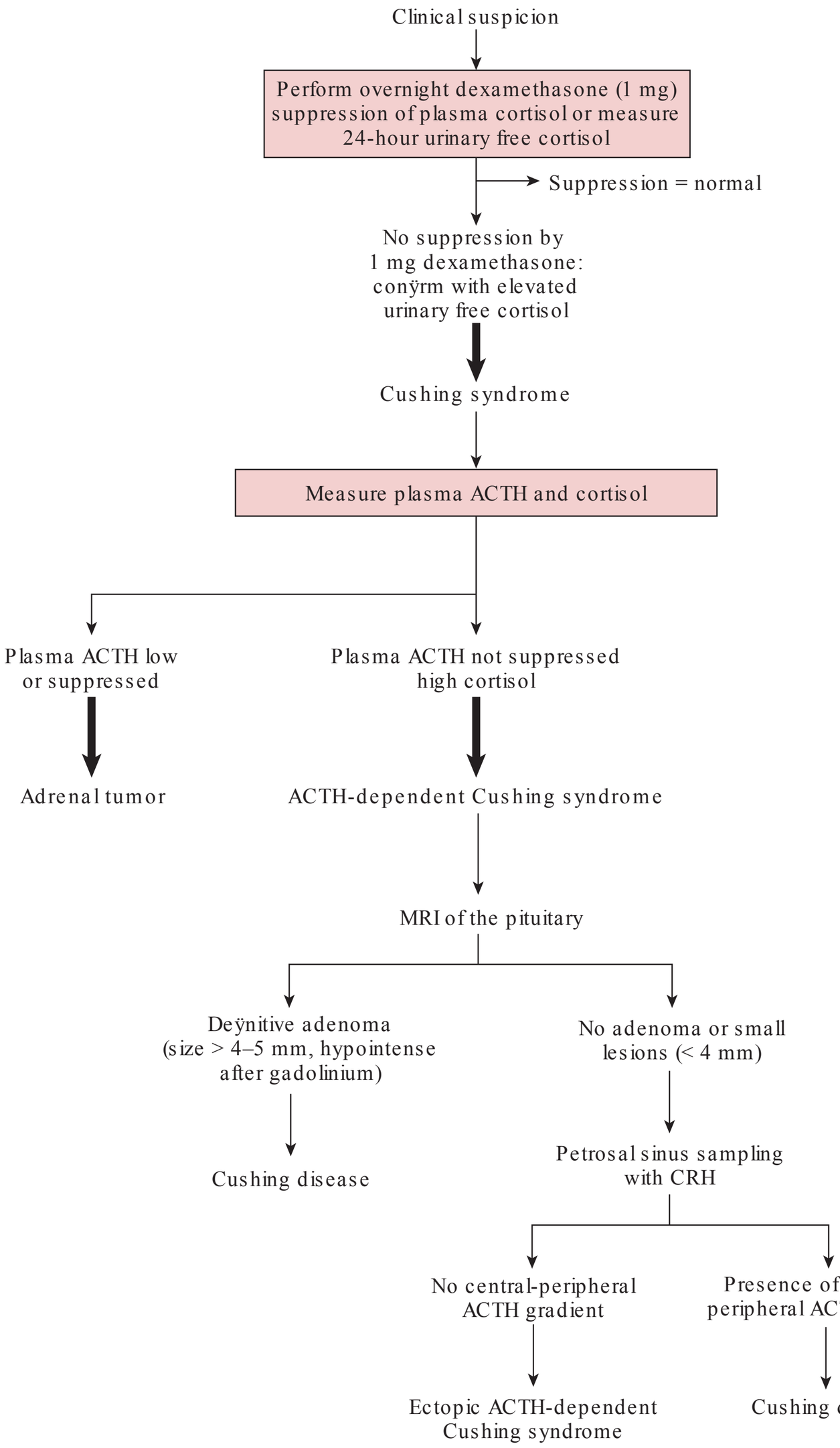


FIGURE 2.3-15. Diagnostic algorithm for Cushing syndrome. (Reproduced with permission from Doherty GM. Current Diagnosis & Treatment: Surgery, 13th ed. New York, NY: McGraw-Hill; 2009.)

History/Pe

- Presents with **enlargement of the skull (frontal bossing, wide-spaced teeth), hands, and feet, coarsening of facial features, large tongue, and skin tags.** Associated with an ↑ risk of carpal tunnel syndrome, obstructive sleep apnea, type 2 DM, heart disease (diastolic dysfunction), hypertension, colon cancer, and arthritis.
- **Bitemporal hemianopsia** may result from compression of the optic chiasm by a pituitary adenoma.

TABLE 2.3-9. Laboratory Findings in Cushing Syndrome

	Cushing disease (pituitary hypersecretion)	Exogenous steroid use	Ectopic ACTH secretion	Adrenal cortisol hypersecretion
24-hour urinary free cortisol	↑	↑	↑	↑
Salivary cortisol	↑	↑	↑	↑
ACTH	↑	↓	↑	↓
Dexamethasone suppression test morning cortisol level:		N/A[a]		N/A[a]
Low dose	↑		↑	
High dose	↓		↑	

[a]A dexamethasone suppression test is not required once the diagnosis of ACTH-independent Cushing syndrome is made.

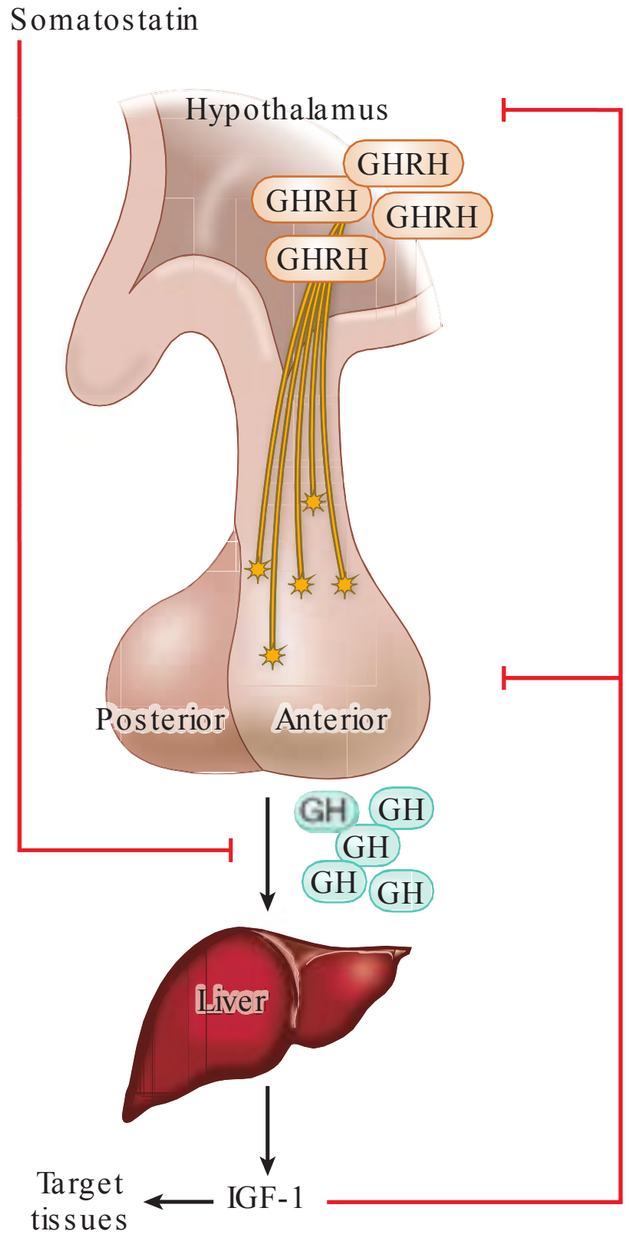


FIGURE 2.3-16. The hypothalamic-pituitary axis: acromegaly.

- Excess GH may also lead to **glucose intolerance, diabetes, and cardiomyopathy.**

Diagnosis

- **Labs: Measure IGF-1 levels (↑ with acromegaly);** confirm the diagnosis with an oral glucose suppression test (GH levels will remain elevated despite glucose administration). Baseline **GH is not a reliable test.**
- **Imaging:** MRI shows a sellar lesion.

KEY FACT

Measure IGF-1 levels to confirm acromegaly, not GH levels!

Treatment

- Transsphenoidal surgical resection or external beam radiation of the tumor.
- Octreotide or lanreotide (somatostatin analogues) can be used to suppress GH secretion; pegvisomant (a GH receptor antagonist) can be used to block the peripheral actions of GH.

Complications

The leading cause of death is from **cardiovascular complications** (CHF).

HYPERPROLACTINEMIA

Elevated prolactin levels, most commonly due to a pituitary adenoma (see Figure 2.3-17). **Prolactinoma is the most common functioning pituitary tumor.** Other causes include pituitary stalk compression from other masses (eg, craniopharyngioma, meningioma, nonsecreting pituitary tumor), drugs (eg, dopamine antagonists), renal failure, and cirrhosis.

History/Pe

Elevated prolactin inhibits GnRH secretion and consequently lowers LH and FSH secretion, manifesting as **infertility, galactorrhea, and amenorrhea.** Bitemporal hemianopsia may also be present.

KEY FACT

Rule out pregnancy in all cases of hyperprolactinemia.

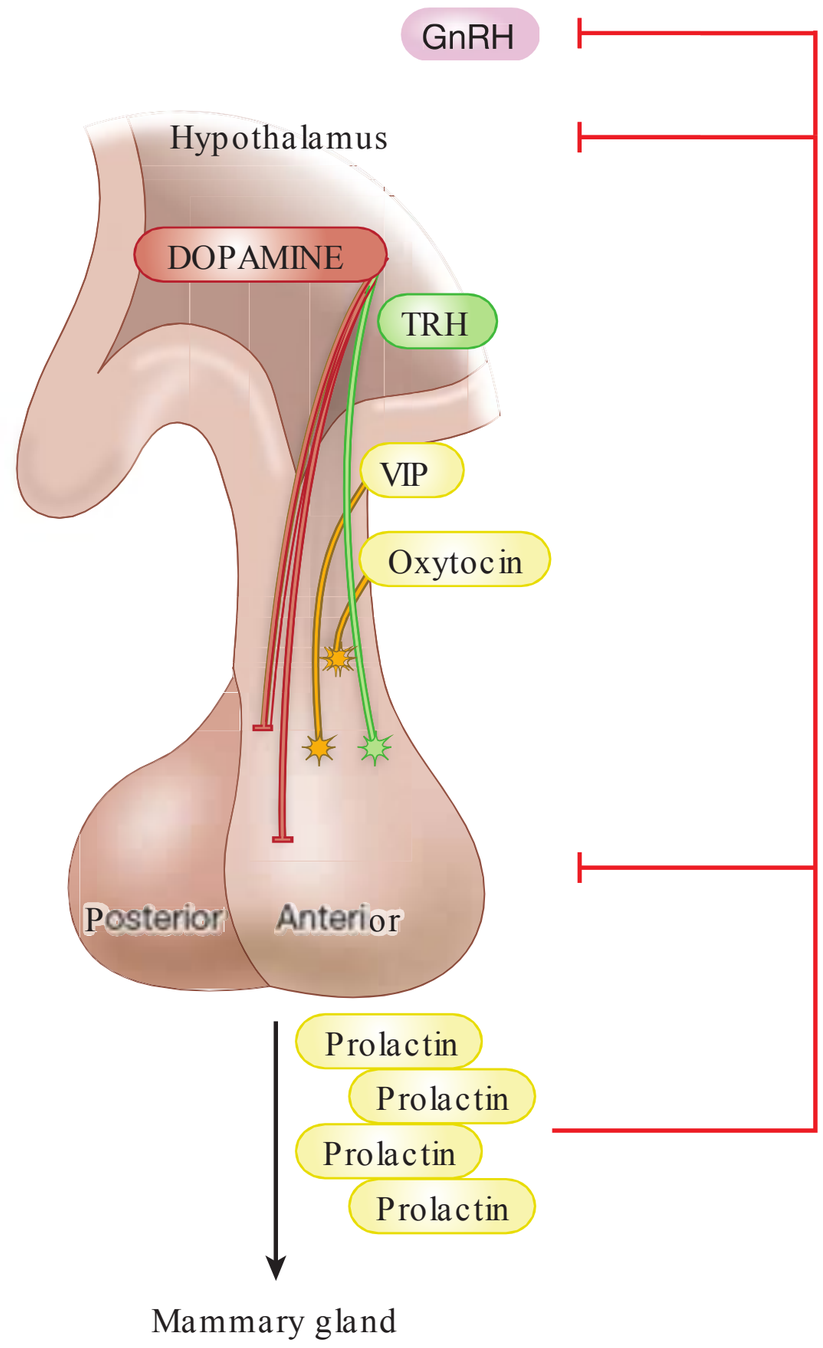


FIGURE 2.3-17. The hypothalamic-pituitary axis: prolactin regulation.

Diagnosis

- The serum **prolactin level is typically > 200 ng/mL.**
- MRI shows a sellar lesion.

Treatment

- **First line:** Dopamine agonists (eg, **cabergoline,** bromocriptine).
- **Surgery:** Indicated in adenomas refractory to medical management or with compressive effects (eg, visual loss).

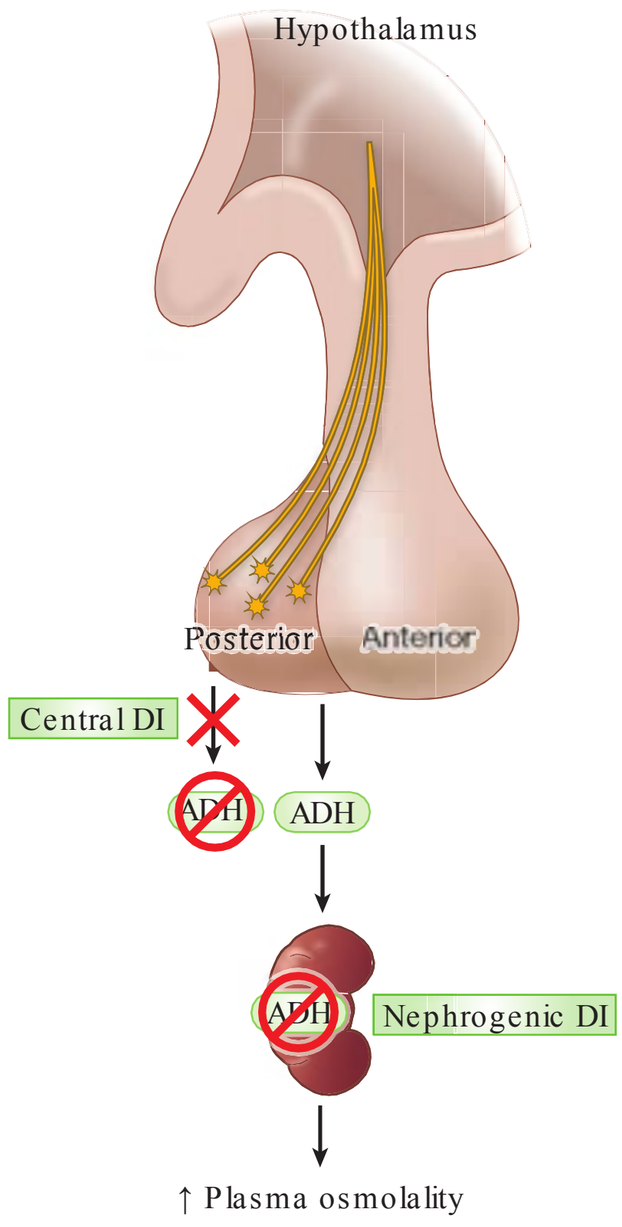


FIGURE 2.3-18. The hypothalamic-pituitary axis: DI.

DIABETES INSIPIDUS (DI)

Inability to produce concentrated urine as a result of ADH dysfunction. The two subtypes are as follows:

- **Central DI (ADH deficiency):** The posterior pituitary fails to secrete ADH. Causes include tumor, ischemia (Sheehan syndrome), pituitary hemorrhage, traumatic brain injury, infection, metastatic disease, and autoimmune disorders (see Figure 2.3-18).
- **Nephrogenic DI (ADH resistance):** The kidneys fail to respond to circulating ADH. Causes include renal disease and drugs (eg, **lithium,** demeclocycline).

History/Pe

- Presents with **polydipsia, polyuria,** and **persistent thirst** with dilute urine. Most cases are normonatremic.
- If access to water is limited (eg, in the institutionalized or elderly), patients may present with dehydration and severe hypernatremia leading to altered mental status, lethargy, seizures, and coma.

Diagnosis

- **Water deprivation test:** In psychogenic polydipsia and normal renal physiology, water restriction will lead to **more concentrated urine.** In central and nephrogenic DI, patients excrete a high volume of **inappropriately dilute urine.**
- **Desmopressin acetate (DDAVP, a synthetic analogue of ADH) replacement test:**
  - **Central DI:** ↓ urine output and ↑ **urine osmolarity** (by 50–100%).
  - **Nephrogenic DI:** No effect is seen on urine output or urine osmolarity.
- MRI may show a pituitary or hypothalamic mass in central DI.

Treatment

- Treat the underlying cause.
- **Central DI:** Administer DDAVP intravenously, intranasally, or orally.
- **Nephrogenic DI:** First-line treatment consists of salt restriction and water intake. Thiazide diuretics can be used to promote mild volume depletion and to stimulate ↑ water reabsorption.

SIADH

A common cause of euvolemic hyponatremia that results from **persistent ADH release independent of serum osmolality** (see Figure 2.3-19).

History/Pe

Associated with **CNS disease** (eg, head injury, tumor), **pulmonary disease** (eg, sarcoid, COPD, pneumonia), ectopic tumor production/paraneoplastic syndrome (eg, small cell lung carcinoma), and drugs (eg, antipsychotics, antidepressants, NSAIDs).

Diagnosis

- Urine osmolality is > 50–100 mOsm/kg in the setting of serum hypoosmolarity **without a physiologic reason for ↑ ADH** (eg, CHF, cirrhosis, hypovolemia).
- **A urinary sodium level is often ≥ 40 mEq/L.**

Treatment

- **Restrict fluid** and address the underlying cause.
- If hyponatremia is severe (< 110 mEq/L) or if the patient is significantly symptomatic (eg, comatose, seizing), **cautiously give hypertonic saline.** Patients must be monitored in the ICU to prevent **central pontine myelinolysis.**
- Demeclocycline, an ADH receptor antagonist, or vasopressin receptor antagonists (conivaptan) can help normalize serum sodium.

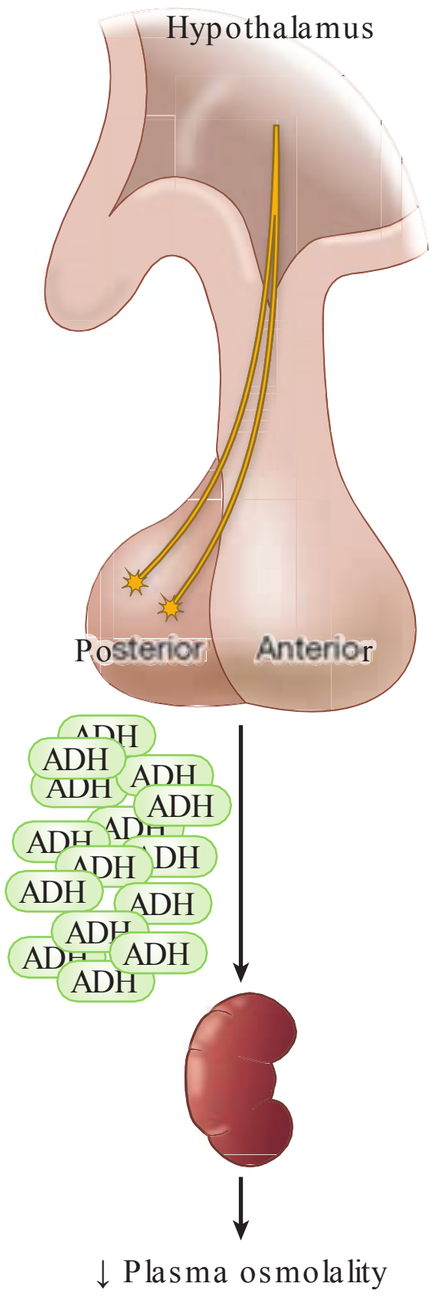


FIGURE 2.3-19. The hypothalamic-pituitary axis: SIADH.

KEY FACT

Fluid restriction is the cornerstone of SIADH treatment.

KEY FACT

Correct hyponatremia slowly to prevent central pontine myelinolysis.

Adrenal Gland Disorders

See Figure 2.3-20 for an overview of adrenal anatomy, regulatory control, and secretory products.

KEY FACT

Dehydroepiandrosterone (DHEAS) is produced **only** by the adrenal gland.

ADRENAL INSUFFICIENCY (AI)

Inadequate production of adrenal hormones, including glucocorticoids and/or mineralocorticoids. May be 1° or 2°/3°. Etiologies are as follows:

- **1°:** In the United States, most commonly due to autoimmune adrenal cortical destruction **(Addison disease).** Other causes include congenital enzyme deficiencies, adrenal hemorrhage (Waterhouse-Friderichsen syndrome from Neisseria meningitidis), and infections (HIV, histoplasmosis, TB). TB is the most common cause of AI worldwide (can see calcification of the adrenal glands).
- **2°/3°:** Caused by ↓ ACTH production by the pituitary or ↓ CRH production by the hypothalamus; **most often due to cessation of long-term glucocorticoid treatment (often > 20 g for > 3 weeks).**

KEY FACT

1° AI is associated with ↑ **skin pigmentation,** ↓ glucocorticoids, and ↓ **mineralocorticoids.** 2° is only associated with ↓ glucocorticoids and does not have skin pigmentation or hyperkalemia.

History/Pe

- Most symptoms are nonspecific.
- **Weakness, fatigue,** and **anorexia with weight loss** are common.
- **Hyperpigmentation** (due to ↑ ACTH secretion) is seen in Addison disease.

Diagnosis

8 AM plasma cortisol levels and **ACTH levels** can lead to a diagnosis (see Table 2.3-10 for laboratory findings). A **synthetic ACTH stimulation (cosyntropin) test** is the test of choice if morning cortisol levels are nondiagnostic.

- An 8 AM plasma cortisol level < 3 µg/dL in the absence of exogenous glucocorticoid administration is diagnostic of AI.
- Failure of cortisol to rise > 20 µg/dL following ACTH administration confirms the diagnosis.

MNEMONIC

The 4 S's of adrenal crisis management—

Salt: 0.9% saline
Steroids: IV hydrocortisone 100 mg every 8 hours
Support
Search for the underlying illness

KEY FACT

Do not delay the administration of steroids in a patient with suspected AI.

Treatment

- **1°:** Glucocorticoid and **mineralocorticoid** replacement.
- **2°/3°:** Only glucocorticoid replacement is necessary **(mineralocorticoid production is not ACTH dependent).**
- In adrenal crisis, provide IV steroids; correct electrolyte abnormalities as

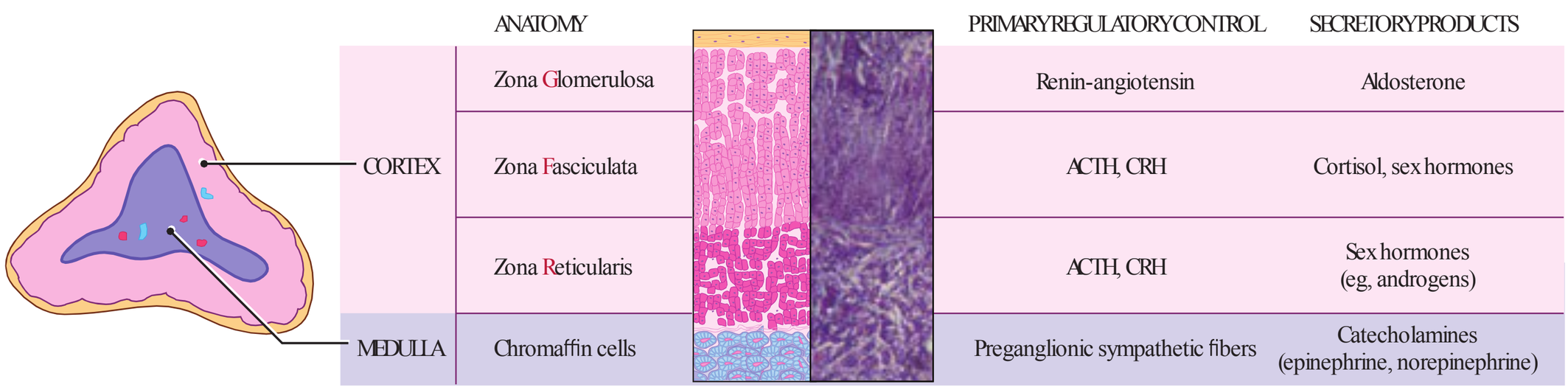


FIGURE 2.3-20. Overview of adrenal anatomy, regulatory control, and secretory products. (Reproduced with permission from USMLE-Rx.com.)

TABLE 2.3-10. Laboratory Findings in Adrenal Insufficiency

	Cortisol	Aldosterone	ACTH	Sodium	Potassium
1° adrenal insufficiency	↓	↓	↑	↓	Nl
2°/3° adrenal insufficiency	↓	**Normal**	↓	Nl/↓	↑

needed; provide 50% dextrose to correct hypoglycemia; and initiate aggressive volume resuscitation.
- ↑ steroids during periods of stress (eg, major surgery, trauma, infection).
- In patients on chronic steroid therapy, taper slowly to prevent 2°/3° AI.

PHEOCHROMOCYTOMA

A tumor of chromaffin tissue that secretes catecholamines and is found either in the adrenal medulla or in extra-adrenal sites. Most commonly associated with **MEN 2A and 2B.**

History/Pe

- Presents with **paroxysmal** tachycardia, palpitations, chest pain, diaphoresis, hypertension, headache, tremor, and anxiety.
- It is important to obtain a family history in order to rule out genetic causes of pheochromocytoma (eg, MEN 2A/2B, von Hippel–Lindau disease, neurofibromatosis).

Diagnosis

- CT and MRI are both sensitive for pheochromocytomas (see Figure 2.3-21). A nuclear MIBG scan can localize extra-adrenal lesions and metastatic disease.
- Look for elevated plasma-free metanephrines (metanephrine and normetanephrine) or 24-hour urine metanephrines and catecholamines.

Treatment

- Surgical resection.
- Preoperatively, use α-adrenergic blockade first (phenoxybenzamine) to control hypertension, followed by β-blockade to control tachycardia. **Never give β-blockade first,** as unopposed α-adrenergic stimulation can lead to severe hypertension.

HYPERALDOSTERONISM

Results from excessive secretion of aldosterone from the zona glomerulosa of the adrenal cortex. It is usually due to adrenocortical hyperplasia (70%) but can also result from unilateral adrenal adenoma **(Conn syndrome).**

History/Pe

- Presents with hypertension, headache, polyuria, and muscle weakness.
- Consider hyperaldosteronism in younger adults who are diagnosed with hypertension without risk factors or a family history of hypertension.

MNEMONIC

Pheochromocytoma rule of 10's—

10% Extra-adrenal
10% Bilateral
10% Malignant
10% Occur in children
10% Familial

MNEMONIC

The 5 P's of pheochromocytoma—

Pressure (BP)
Pain (headache)
Perspiration
Palpitations
Pallor

Q 1

A 23-year-old man with a history of schizophrenia presents with complaints of fatigue, weakness, cramps, and headache for the past several days. He denies any other symptoms, although he had to urinate several times while in the office. Routine labs reveal hyponatremia. With water deprivation, his urine osmolality ↑. What is the most likely diagnosis?

Q 2

An asymptomatic 36-year-old woman presents with a 2-cm thyroid mass. TFTs are unremarkable, but FNA reveals medullary carcinoma. Total thyroidectomy with thyroid hormone replacement is recommended. What is the most important screening test to perform prior to surgery?

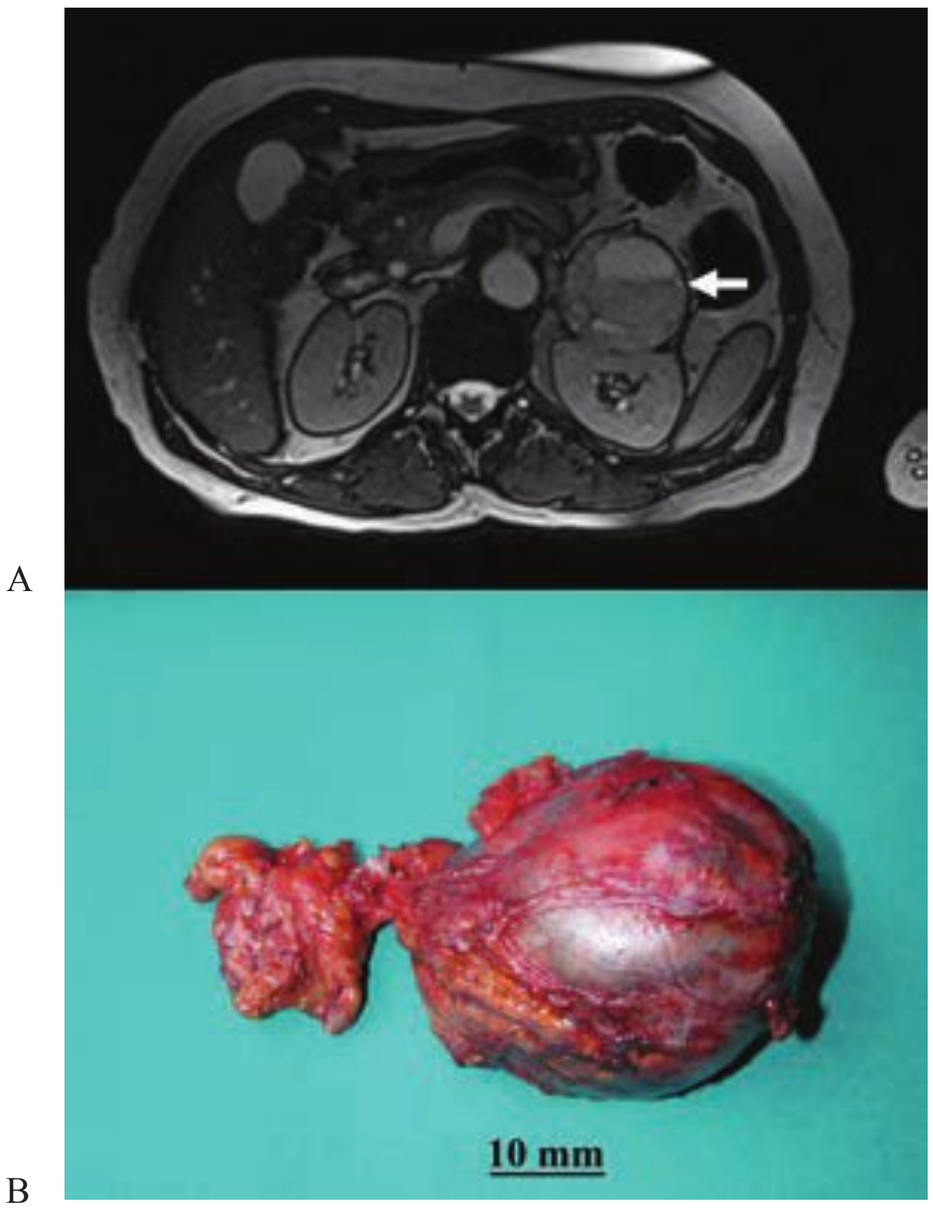


FIGURE 2.3-21. Pheochromocytoma. (A) MRI showing left supra-renal mass. **(B)** Pheochromocytoma postsurgical resection. (Reproduced with permission from Roghi A et al. Adrenergic myocarditis in pheochromocytoma, J Cardiovasc Magn Reson 2011 Jan 11;13:4.)

KEY FACT

In pheochromocytoma, administer α-blockers before β-blockers to prevent hypertensive crisis.

1 A

1° (psychogenic) polydipsia, a condition in which patients consume large volumes of fluid, resulting in polyuria. It most often occurs in patients with psychiatric disorders. Patients present with symptoms similar to DI, but following a water deprivation test, urine osmolality ↑ (vs DI, in which urine remains dilute).

2 A

VMA and metanephrines. Medullary carcinoma of the thyroid is associated with MEN type 2A/2B, an autosomal dominant condition that predisposes patients not only to medullary carcinoma but also to parathyroid adenomas and pheochromocytomas. Screening for pheochromocytoma with urine VMA and metanephrines prior to surgery can prevent potentially life-threatening hypertensive crises during thyroidectomy.

Diagnosis

- Labs show **hypokalemia,** metabolic **alkalosis,** hypomagnesemia, hyperaldosteronism, and an ↑ **aldosterone-to-plasma renin activity ratio** (usually > 30).
- CT or MRI may reveal an adrenal mass. Adrenal venous sampling may be needed to localize the adenoma or to confirm bilateral adrenal hyperplasia.

Treatment

- Surgical resection for adrenal tumors (after correction of BP and potassium).
- Treat bilateral hyperplasia with an aldosterone receptor antagonist (**eplerenone** preferred over spironolactone as has fewer side effects).

CONGENITAL ADRENAL HYPERPLASIA

Inherited enzyme defects that impair cortisol synthesis and result in the accumulation of cortisol precursors. Most cases are due to **21-hydroxylase deficiency** (95%, autosomal recessive), but other causes include 11- and 17-hydroxylase deficiencies.

History/Pe

See Table 2.3-11.

TABLE 2.3-11. Overview of Congenital Adrenal Hyperplasia

Enzyme deficiency	Mineralocorticoids	Cortisol	Sex hormones	bp	$[K^+]$	labs	presentation
17α-hydroxylase[a]	↑	↓	↓	↑	↓	↓ androstenedione	XY: pseudohermaphroditism (ambiguous genitalia, undescended testes) XX: lack secondary sexual development
21-hydroxylase[a]	↓	↓	↑	↓	↑	↑ renin activity ↑ 17-hydroxyprogesterone	Most common Presents in infancy (salt wasting) or childhood (precocious puberty) XX: virilization
11β-hydroxylase[a]	↓ aldosterone ↑ 11-deoxycorticosterone (results in ↑ BP)	↓	↑	↑	↓	↓ renin activity	XX: virilization

[a]All congenital adrenal enzyme deficiencies are characterized by an enlargement of both adrenal glands due to ↑ ACTH stimulation (due to ↓ cortisol).

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Diagnosis

- Electrolyte abnormalities include hyponatremia, hyperkalemia, and metabolic acidosis. In severe cases, mineralocorticoid deficiency may lead to life-threatening salt wasting.
- An **elevated serum 17-hydroxyprogesterone level** is diagnostic of 21-hydroxylase deficiency.

Treatment

- **Medical: Immediate fluid resuscitation and salt repletion.** Administer cortisol to ↓ ACTH and adrenal androgens. Fludrocortisone is appropriate for severe 21-hydroxylase deficiency.
- **Possible surgical correction of ambiguous genitalia.**
- Refer to the Gynecology chapter for information on the diagnosis and treatment of late-onset CAH.

Multiple Endocrine Neoplasias

A family of tumor syndromes with autosomal dominant inheritance (see Figure 2.3-22).

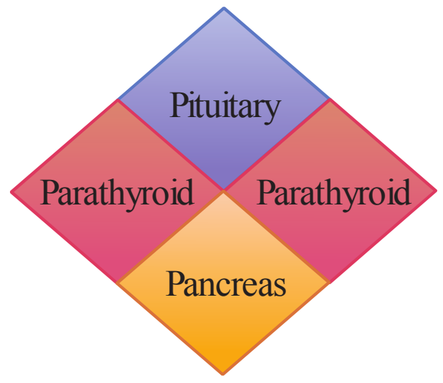
- **MEN type 1 (Wermer syndrome):** Pancreatic islet cell tumors (eg, **gastrinomas** [Zollinger-Ellison syndrome], insulinomas, VIPomas), parathyroid hyperplasia, and pituitary adenomas.

MNEMONIC

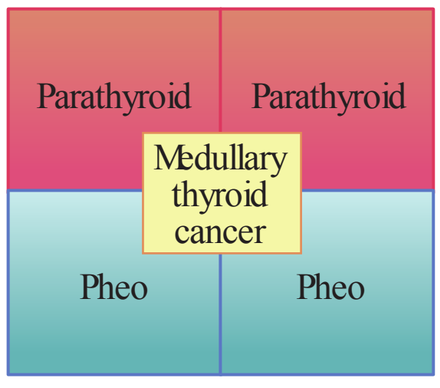
MEN 1 affects "P" organs—

Pancreas
Pituitary
Parathyroid

MEN 1 = **3 P's**: **P**ituitary, **P**arathyroid, and **P**ancreas; remember by drawing a diamond.



MEN 2A = **2 P's**: **P**arathyroids and **P**heochromocytoma; remember by drawing a square.



MEN 2B = **1 P**: **P**heochromocytoma; remember by drawing a triangle.

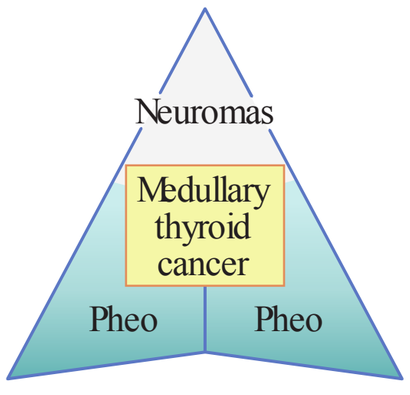


FIGURE 2.3-22. Multiple endocrine neoplasias (MEN). (Reproduced with permission from Le T, Bhushan V. First Aid for the USMLE Step 1 2015: A Student-to-Student Guide. New York, NY: McGraw-Hill; 2015.)

- **MEN type 2A (Sipple syndrome):** Medullary carcinoma of the thyroid, pheochromocytoma or adrenal hyperplasia, parathyroid gland hyperplasia. Due to mutations in the **RET proto-oncogene.**
- **MEN type 2B:** Medullary carcinoma of the thyroid, pheochromocytoma, oral and intestinal ganglioneuromatosis (mucosal neuromas), marfanoid habitus. Due to mutations in the **RET proto-oncogene.**

HIGH-YIELD FACTS IN

EPIDEMIOLOGY

Assessment of Disease Frequency 112

Assessment of Diagnostic Studies 112

- Sensitivity and Specificity 112
- Positive and Negative Predictive Values 113
- Likelihood Ratio 113

Measures of Effect 113

Survival Curves 114

Types of Clinical Studies 114

- Cross-Sectional Studies 115
- Cohort Studies 115
- Case-Control Studies 116
- Randomized Controlled Trials 116

Evaluating Clinical Studies 117

- Bias 117
- Chance 118
- Prevention 119
- Vaccination 119

Behavioral Counseling 120

Screening Recommendations 122

Causes of Death 123

Reportable Diseases 124

Assessment of Disease Frequency

KEY FACT

Incidence can be measured in a cohort study; prevalence can be measured in a cross-sectional study.

The **prevalence** of a disease is the number of existing cases in the population at a specific moment in time.

$$\text{Prevalence} = \frac{\text{total number of cases in the population at one point in time}}{\text{total population}}$$

- The **incidence** of a disease is the number of new cases in the disease-free population that develop over a period of time.

$$\text{Incidence} = \frac{\text{number of } \textbf{new} \text{ cases in the population over a given time period}}{\text{total population at risk during the specified time period}}$$

- Prevalence depends on incidence and duration:

$$\text{Prevalence (P)} = \text{incidence (I)} \times \text{average duration of disease (D)}$$

- For incidence, remember to subtract any preexisting cases of the disease from the total population at risk, as these individuals are no longer at risk.

KEY FACT

As the mortality of a disease ↓, the prevalence of that disease ↑ (eg, HIV infection), because the duration of disease has lengthened. Remember: P = I × D.

Assessment of Diagnostic Studies

SENSITIVITY AND SPECIFICITY

Physicians often use tests to narrow and confirm possible diagnoses. The **sensitivity** and **specificity** of these tests allow physicians to determine how often false positives and negatives occur (see Figure 2.4-1).

- **Sensitivity:** The probability that a patient with a disease will have a ⊕ test result.
  - A sensitive test will **rarely miss people** with the disease and is therefore good at **ruling out those who do not have the disease.**
  - Desirable early in a **diagnostic workup or screening test,** when it's necessary to reduce a broad differential diagnosis.
  - **Example:** An initial ELISA test for HIV infection.

$$\text{False-}\ominus \text{ ratio} = 1 - \text{sensitivity}$$

- **Specificity:** The probability that a patient without a disease will have a ⊖ test result.
  - A specific test will rarely determine that someone has the disease when in fact they do not and is therefore good at **ruling in those who have the disease.**
  - Desirable when **confirming a likely diagnosis.**
  - **Example:** A Western blot confirmatory HIV test.

$$\text{False-}\oplus \text{ ratio} = 1 - \text{specificity}$$

MNEMONIC

SNOUT—**S**e**N**sitive tests rule **OUT** disease.
SPIN—**SP**ecific tests rule **IN** disease.

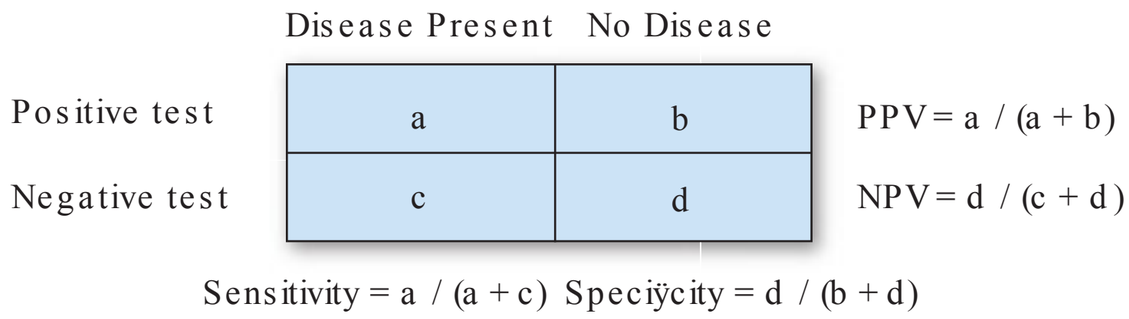


FIGURE 2.4-1. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

- The ideal test is both sensitive and specific, but a trade-off must often be made between sensitivity and specificity (see Figure 2.4-2). For a given test, when sensitivity ↑, specificity ↓ (and vice versa).

POSITIVE AND NEGATIVE PREDICTIVE VALUES

Once a test has been administered and a patient's result has been made available, that result must be interpreted through use of predictive values:

- **PPV:** The probability that a patient with a ⊕ test result truly **has** the disease. **The higher the disease prevalence, the higher the PPV of the test for that disease.**
- **NPV:** The probability that a patient with a ⊖ test result truly **does not have** the disease. **The lower the disease prevalence, the higher the NPV of the test for that disease.**

LIKELIHOOD RATIO

LRs express the extent to which a given test result is likely in diseased people as opposed to people without disease:

- ⊕ **LR** shows how much the odds (or probability) of disease are ↑ if the test result is ⊕.
- ⊖ **LR** shows how much the odds (or probability) of disease are ↓ if the test result is ⊖.

Posttest odds = pretest odds × LR

Measures of Effec

There are several ways to express and compare risk. These include the following:

- **Absolute risk:** The incidence of disease.
- **Attributable risk (or risk difference):** The difference in risk between the exposed and unexposed groups.

Attributable risk = incidence of disease in exposed − incidence in unexposed.

- **Number needed to treat:** Number of individuals that need to be treated for 1 patient to benefit.

Number need to treat (NNT) = 1 / attributable risk

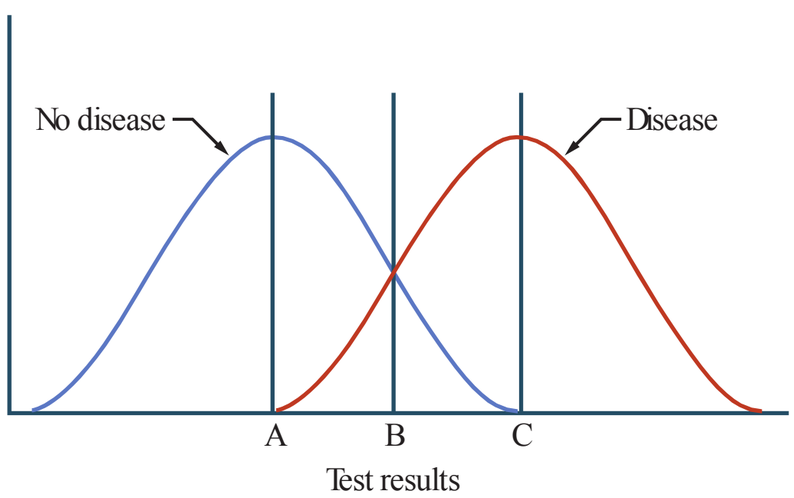


FIGURE 2.4-2. Effect of cutoff values on sensitivity and specificit (Adapted with permission from USMLE-RX.com.)

- **Relative risk (or risk ratio; RR):** Expresses how much more likely an exposed person is to get the disease in comparison to an unexposed person. This indicates the **relative strength of the association between exposure and disease,** making it useful when one is considering disease etiology.

$$\text{Relative risk} = \frac{\text{incidence in exposed}}{\text{incidence in unexposed}}$$

RR > 1 suggest an increased risk

RR < 1 suggests an decreased risk

- **Odds ratio (OR):** An **estimate of relative risk that is used in case-control studies.** The OR tells how much more likely it is that a person with a disease has been exposed to a risk factor than someone without the disease. **The lower the disease incidence, the more closely it approximates RR.** In case-control studies, the OR also describes how many times more likely an exposed individual is to have disease compared to an unexposed individual (see Figure 2.4-3).

$$\text{Odds ratio} = \frac{\text{odds that a diseased person is exposed}}{\text{odds that a nondiseased person is exposed}}$$

Survival Curves

Once a diagnosis has been established, it is important to be able to describe the associated prognosis. **Survival analysis is used to summarize the average time from one event** (eg, presentation, diagnosis, or start of treatment) **to any outcome that can occur only once during follow-up** (eg, death or recurrence of cancer). The usual method is with a **Kaplan-Meier curve** (see Figure 2.4-4) describing the survival in a cohort of patients, with the probability of survival decreasing over time as patients die or drop out from the study.

Types of Clinical Studies

Studies are typically used to evaluate diagnosis, treatment, and screening for a disease. Although **the gold standard for such evaluation is a randomized, double-blinded controlled trial,** other types of studies may be used as well (eg, an observational study, in which the exposure in question is a therapeutic intervention). In descending order of quality, published studies regarding treatment options include randomized controlled trials (RCTs), observational studies, and case series/case reports. Meta-analyses are often used to systematically synthesize information across studies to help summarize the totality of the evidence.

KEY FACT

Randomization minimizes bias and confounding; double-blinded studies prevent observation bias.

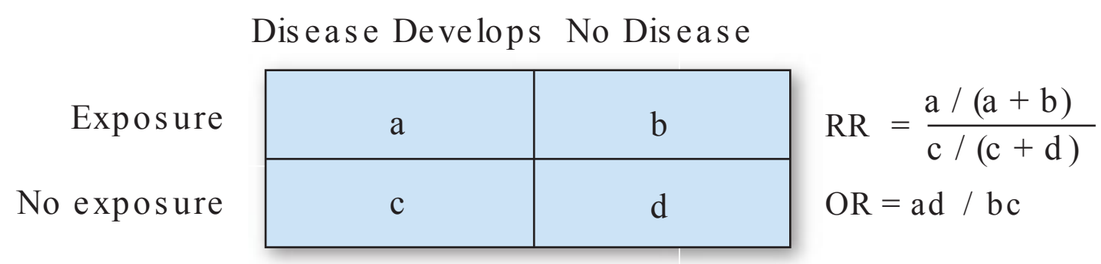


FIGURE 2.4-3. Relative risk (RR) vs odds ratio (OR).

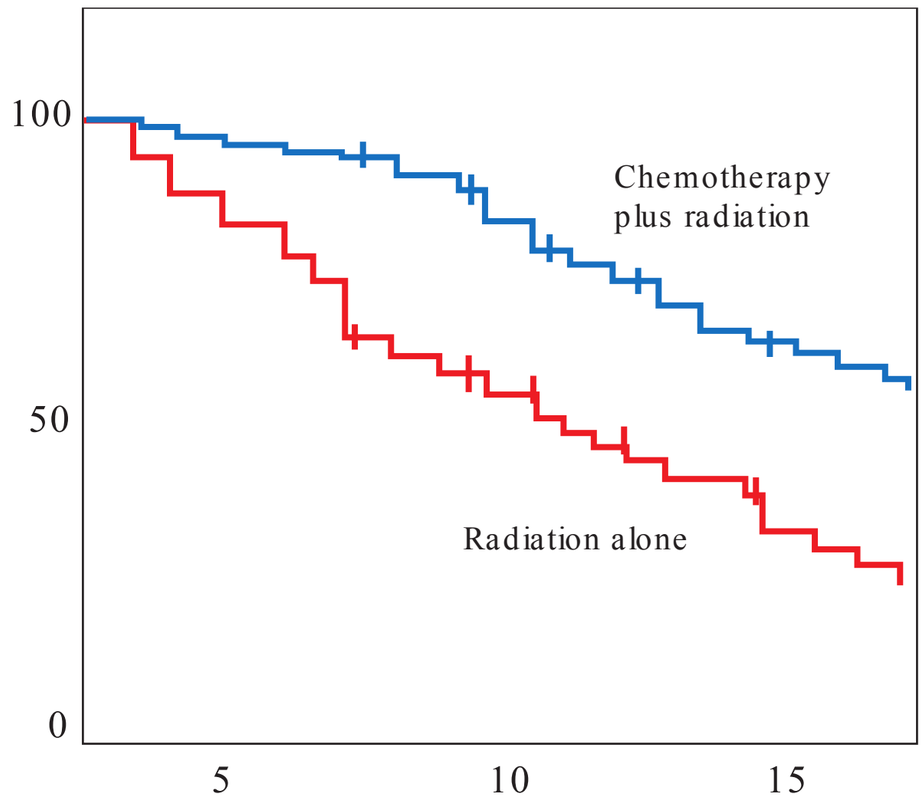


FIGURE 2.4-4. Example of a Kaplan-Meier curve.

CROSS-SECTIONAL STUDIES

A **cross-sectional** study is an observational study that assesses risk factors and outcomes at a snapshot in time. These studies aren't able to prove temporal relationships, because they measure correlation, not causation.

- The **advantages** of cross-sectional studies are as follows:
  - They provide an efficient means of examining a population, allowing simultaneous assessment of people with the disorder and those without it.
  - They can be used as a basis for diagnostic testing.
- Their **disadvantages** include the following:
  - One cannot determine causal relationships, because information is obtained only at a **single point in time.**
  - The risk or incidence of disease cannot be directly measured.

KEY FACT

A cross-sectional study that is undertaken to estimate prevalence is called a **prevalence study.**

COHORT STUDIES

In a **cohort study,** a group of people is assembled, **none of whom has the outcome of interest** (ie, the disease), but **all of whom could potentially experience that outcome.** For each possible risk factor, the members of the cohort are classified as either exposed or unexposed. All the cohort members are then followed over time, and the **incidence of outcome events is compared in the two exposure groups. Example:** The Framingham Heart Study followed a group of men and women over time to see how different exposures (diet, exercise, aspirin, etc.) affected the incidence of heart disease.

- **Advantages** of cohort studies are as follows:
  - They are the only way to **directly determine incidence** (because they follow a cohort over time to assess disease development).
  - They can be used to assess the relationship of a given exposure to many diseases.
  - In prospective studies, exposure is elicited without bias from a known outcome.

Q 1

A local child-care center that was built before the 1950s was found to have elevated lead levels in its paint. A student organization at your medical school is hosting a lead-screening event to test all the children at the center. Which initial screening test would be more appropriate: a test that has high sensitivity or one that has high specificity?

Q 2

What happens to the PPV and NPV when prevalence ↓?

KEY FACT

Cohort studies are also known as longitudinal studies or incidence studies.

KEY FACT

In **cohort studies,** the researcher determines whether the participants are exposed or unexposed and follows them over time for disease development.

KEY FACT

In **case-control studies,** the researcher determines whether the participants have the disease or not and determines if they were exposed or unexposed.

- **Disadvantages** of cohort studies include the following:
  - They can be **time consuming** and **expensive.**
  - Studies assess only the relationship of the disease to the few exposure factors recorded at the start of the study.
  - Their requirement for many subjects makes it difficult to study rare diseases.

Cohort studies can be either **prospective,** in which a cohort is assembled in the present and followed into the future, or **retrospective,** in which a cohort is identified from past records and is followed to the present.

CASE-CONTROL STUDIES

In **case-control studies,** a series of **cases** are identified and a set of **controls** are sampled from the underlying population to estimate the frequency of exposure in the population at risk of the outcome. In such studies, a researcher **compares the frequency of exposure to a possible risk factor** between the case and control groups. **Example:** A study examines patients with heart disease (cases) and without heart disease (controls) and compares exposures to red meat between both groups.

- The validity of a case-control study depends on appropriate selection of cases and controls, the manner in which exposure is measured, and the manner in which extraneous variables (confounders) are dealt with**.**
- Cases and controls should be comparable in terms of opportunity for exposure (ie, they should be members of the same base population with an equal opportunity of risk factor exposure).
- **"Matching"** in case-control studies occurs when the researcher chooses controls that match cases on a particular characteristic. For example, if matching on gender, female cases would be matched to female controls and male cases would be matched to male controls. The purpose of matching is to ↓ confounding.
- **Advantages** of case-control studies are as follows:
  - They use smaller groups than cohorts, thereby reducing cost.
  - They can be used to study rare diseases and can easily examine multiple risk factors.
- **Disadvantages** include the following:
  - Studies cannot calculate disease prevalence or incidence or directly estimate the relative risk, because the numbers of subjects with and without a disease are determined artificially by the investigator rather than by nature; **however, an OR can be used to estimate a measure of RR, if the prevalence is low.**
  - Retrospective data can be inaccurate as a result of recall or survivorship biases.

RANDOMIZED CONTROLLED TRIALS

An experimental, prospective study in which subjects are randomly assigned to a treatment or control group. Random assignment helps remove confounding and ensure that the two groups are truly comparable. The control group may be treated with a placebo or with the accepted standard of care. The study can be masked in one of two ways: single blinded, in which patients do not know which treatment group they are in, or **double blinded,** in which neither the patients nor their physicians know who is in which group. **Double-blinded studies are the gold standard** for studying treatment effects. **Example:** A trial studies the role of aspirin in preventing MI by giving one randomized group a baby aspirin daily and the control group a placebo. The rates of MI are then measured.

1 A

A test with high sensitivity such as a fingerstick lead test (capillary blood) is preferred for initial screening, because it can ensure that no children who might have the disease—and who might therefore benefit from further testing and treatment—will be missed. The children with a ⊕ fingerstick test should subsequently have a serum blood level drawn (higher specificity).

2 A

PPV↓ and NPV↑. Remember that if prevalence is low, even a test with high sensitivity or specificity will have a low PPV.

- **Advantages** of RCTs are as follows (see also Table 2.4-1):
  - Minimize bias.
  - Have the potential to demonstrate **causal relationships,** because exposure is assigned randomly, which minimizes confounding.
- **Disadvantages** include the following:
  - Costly and time intensive.
  - Some interventions (eg, surgery) are not amenable to masking.

Evaluating Clinical Studies

BIAS

Any process that causes results to systematically differ from the truth. Common types of bias include the following:

TABLE 2.4-1. Comparison of Study Designs

Variable	RCT	Cohort	Cross-Sectional	Case Control
Purpose	Tests causality through random assignment of exposure.	Follows groups of patients over a specified period of time to capture the association of risk factors to the development of disease.	Determines prevalence in a snapshot of time.	Tests association (usually retrospectively).
Measures	Any measures that are reported suggest causal relationships.	RR, OR, incidence, prevalence.	Prevalence (not incidence).	OR
Design	Subjects are randomly assigned to be in exposed (treatment A) or unexposed (treatment B) groups.	Subjects are not assigned to groups. Determines if subjects are in exposed or unexposed groups and follows them until they develop the disease (or do not).	Determines disease prevalence at 1 point in time; cannot determine the directionality of association between exposure and outcome.	Identifies cases (disease) and controls (no disease) groups first and then goes backward to determine if they are exposed or not (the opposite of RCT and cohort studies).
Advantages	Can determine causality; minimizes bias and confounding.	Temporality can be determined; incidence can be determined.	Less time consuming and costly.	Predetermined number of cases; less time consuming and costly.
Disadvantages	RCT is not possible when: - The treatment has an adverse outcome. - The outcome is very rare. - The treatment is in widespread use or represents the best option (because it is unethical to withhold treatment).	Follows large groups over long time periods. Selection bias in retrospective cohort studies.	Directionality of association cannot be determined. Incidence cannot be determined.	Recall bias, selection bias.

KEY FACT

Studies that are masked and randomized are better protected from the effects of bias, whereas observational studies are particularly susceptible to bias.

- **Selection bias:** Occurs when samples or participants are selected that differ from other groups in additional determinants of outcome. **Example:** Individuals concerned about a family history of breast cancer may be more likely to self-select in entering a mammography program, giving the impression of a prevalence that is higher than it is in reality.
- **Measurement bias:** Occurs when measurement or data-gathering methods differ between groups. **Example:** One group is assessed by CT while another group is assessed by MRI.
- **Confounding bias:** Occurs when a third variable is either positively or negatively associated with both the exposure and outcome variables, inducing an incorrect association. **Example:** Fishermen in an area may experience a higher incidence of lung cancer than that found in the general population. However, if smokers are more likely to become fishermen and are also more likely to develop lung cancer than nonsmokers, becoming a fisherman will not in itself lead to lung cancer. Rather, it is the smoking to which those fishermen are exposed that causes the association.
  - **Effect modification,** on the other hand, occurs when a third variable disproportionately affects two groups. Effect modification shows a meaningful difference, whereas confounding does not. **Example:** A new chemotherapeutic agent is shown to improve survival in non-Hodgkin lymphoma, but only in patients who are undergoing radiation therapy, whereas those not receiving radiation show no benefit.
- **Recall bias:** Results from a difference between two groups in the retrospective recall of past factors or outcomes. **Example:** A patient with cancer may be more motivated than would a healthy individual to recall past episodes of chemical exposure.
- **Lead-time bias:** Results from earlier detection of disease, giving an appearance of prolonged survival when in fact the natural course is not altered. **Example:** A new and widely used screening test that detects cancer 5 years earlier may yield the impression that patients are living longer with the disease.
- **Length bias:** Occurs when screening tests detect a disproportionate number of slowly progressive diseases but miss rapidly progressive ones, leading to overestimation of the benefit of the screen. **Example:** A better prognosis for patients with cancer is celebrated following the implementation of a new screening program. However, this test disproportionately detects slow-growing tumors, which generally tend to be less aggressive.

KEY FACT

Confounding variables reduce the internal validity of a study.

CHANCE

Even with bias reduction, unsystematic random error is unavoidable because of chance variation in studied data. Types of errors are as follows:

- **Type I (α) error:**
  - The probability of **concluding that there is a difference** in treatment effects between groups **when in fact there is not** (ie, a false-⊕ conclusion)—in other words, rejecting the null hypothesis (of no effect) when it should not be rejected.
  - The **p-value** is an estimate of the probability that differences in treatment effects in a study **could have happened by chance alone if no true association exists.** Often, differences associated with a $p < 0.05$ are statistically significant. A p-value alone **does not give any information about the direction or size of the effect.**
- **Type II (β) error:**
  - The probability of **concluding that there is no difference** in treatment effects **when in fact a difference exists** (ie, a false-⊖ conclusion)—in

other words, **not** rejecting the null hypothesis (of no effect) when it should be rejected.
- **Power** is the probability that a study will find a statistically significant difference when one is truly there. Increasing the number of subjects in a study ↑ the power.

$$\text{Power} = 1 - \text{type II error } (\beta)$$

- The **confidence interval (CI)** is a way of expressing statistical significance (p-value) that shows the **size of the effect and the statistical power (the narrower the CI, the greater the statistical power).** CIs are interpreted as follows:
  - If one is using a 95% CI, there is a **95% chance that the interval contains the true value.**
  - **Larger sample sizes produce more power and narrower CIs.** If the CI includes the null value (RR or OR of 1.0 or 0%), the results are not statistically significant.
  - **Example:** An RCT studying aspirin to prevent myocardial infarction shows a relative risk of 0.9 with a 95% CI of 0.85 to 0.95 in a sample of 3000 patients, whereas in a sample of 30 patients the 95% CI is 0.1 to 1.7. The first example shows a significant difference, whereas the second does not.

PREVENTION

- There are three levels of prevention:
  - **1° prevention:** Includes preventive measures to ↓ the incidence of disease.
  - **2° prevention:** Focuses on identifying the disease early, when it is asymptomatic or mild, and implementing measures that can halt or slow disease progression. Includes screening tests that are designed to identify subclinical disease.
  - **3° prevention:** Includes measures that ↓ morbidity or mortality resulting from the presence of disease.
- Prevention may be accomplished by a **combination of immunization, chemoprevention, behavioral counseling, and screening. A good screening test** has the following characteristics:
  - It has **high sensitivity and specificity** (usually more important to have high sensitivity to **rule out** those who don't have the disease).
  - It has a **high PPV.**
  - It is inexpensive, easy to administer, and safe.
  - Treatment after screening is more effective than subsequent treatment without screening.

VACCINATION

- Vaccines work by mimicking infections and triggering an immune response in which memory cells are formed to recognize and fight any future infection. There are several different vaccine formulations, as indicated in Table 2.4-2.
- Recommended vaccination schedules for children and adults are outlined in Figures 2.4-5 and 2.4-6.
- **Live vaccines should not be administered to immunosuppressed patients.** They are also **contraindicated in pregnant women** owing to a theoretical risk of maternal-fetal transmission. A possible exception to this rule can be some asymptomatic HIV/AIDS patients who may be candidates for the MMR vaccine.

Q

Assume that the data below are from a hypothetical case-control study. Calculate and interpret the OR.

	Exposed	Not exposed
Cases	734	433
Controls	563	538

KEY FACT

- **1° prevention:** A woman reduces dietary intake of fat or alcohol to reduce her risk of developing breast cancer.
- **2° prevention:** A woman obtains a mammogram to screen for breast cancer.
- **3° prevention:** A woman undergoes adjuvant therapy with tamoxifen for breast cancer.

A

OR = ad / bc = (734 × 538) / (433 × 563) = 1.62
Interpretation: The exposed group had 1.62 times the odds of having disease compared to the unexposed group.

TABLE 2.4-2. Types of Vaccinations

Vaccine type	Targeted diseases
Live attenuated	Measles, mumps, rubella, polio (Sabin), yellow fever, influenza (nasal spray).
Inactivated (killed)	Cholera, HAV, polio (Salk), rabies, influenza (injection).
Toxoid	Diphtheria, tetanus.
Subunit	HBV, pertussis, Streptococcus pneumoniae, HPV, meningococcus.
Conjugate	Hib, S pneumoniae.

Behavioral Counseling

In offering counsel, physicians should tailor their education and suggestions to the individual patient as well as to his or her **stage of change** (see Table 2.4-3).

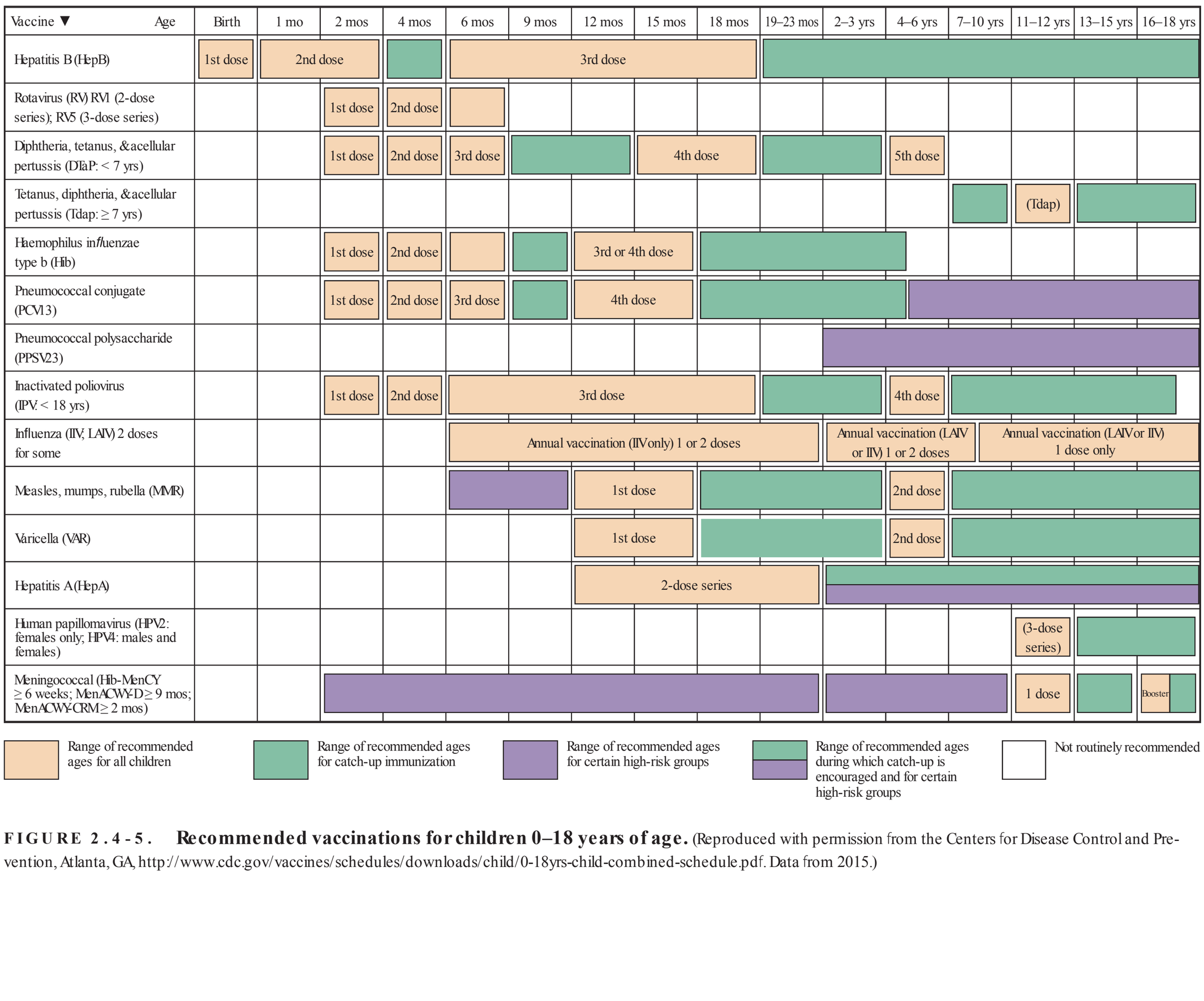


FIGURE 2.4-5. Recommended vaccinations for children 0–18 years of age. (Reproduced with permission from the Centers for Disease Control and Prevention, Atlanta, GA, http://www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-child-combined-schedule.pdf. Data from 2015.)

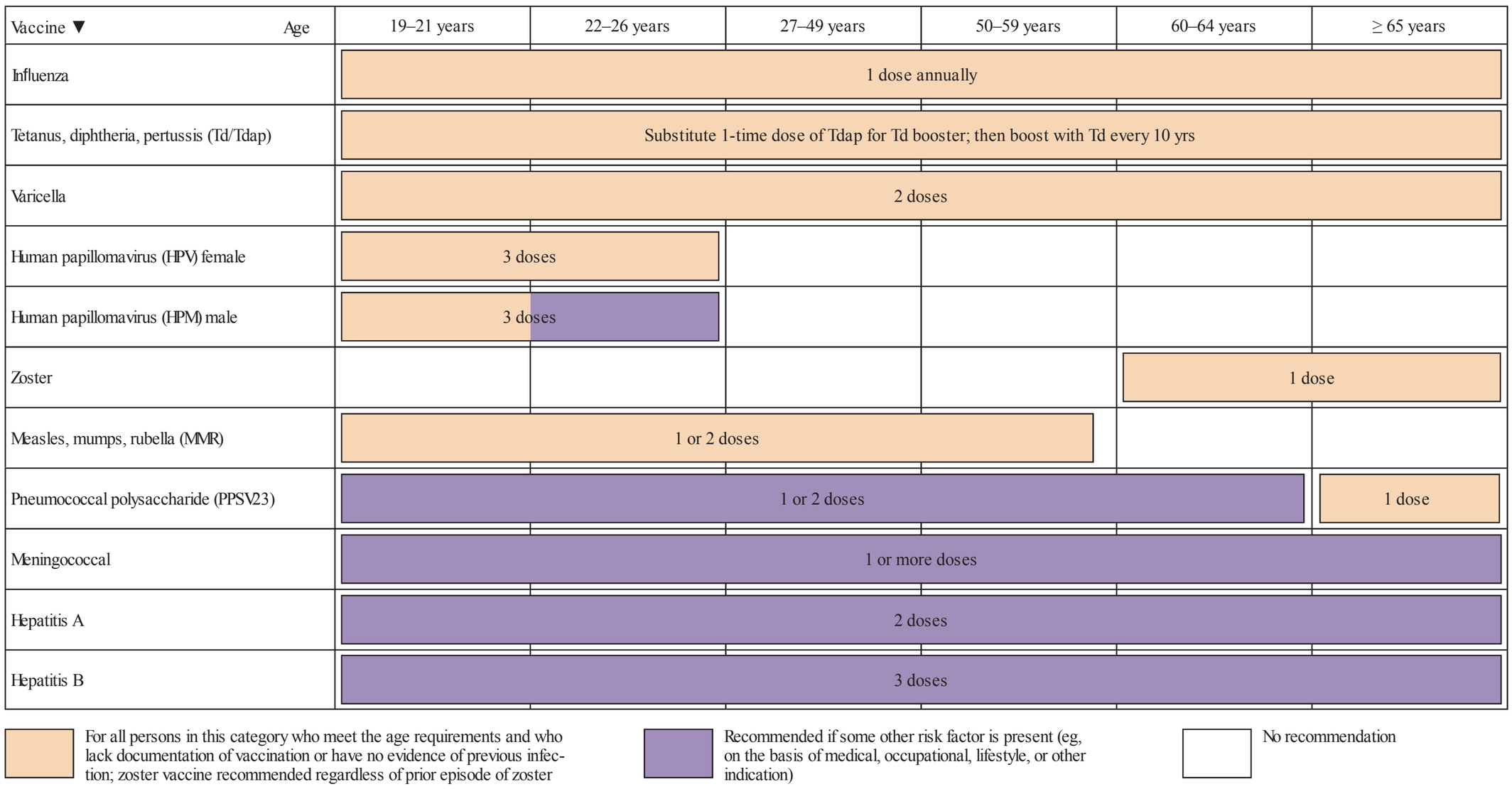


FIGURE 2.4-6. Recommended vaccinations for adults. (Reproduced with permission from the Centers for Disease Control and Prevention, Atlanta, GA, http://www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf. Data from 2015.)

TABLE 2.4-3. Stages of Change in Behavioral Counseling

Stage of Change	Characterization	Example
Precontemplation	Denial or ignorance of the problem.	A heroin addict has not even thought about cessation.
Contemplation	Ambivalence or confli ted emotions; assessing benefits and barriers to change.	The heroin addict considers treatment for his addiction.
Preparation	Experimenting with small changes; collecting information about change.	The heroin addict visits his doctor to ask questions about quitting.
Action	Taking direct action toward achieving a goal.	The addict enters a rehabilitation facility for treatment of addiction.
Maintenance	Maintaining a new behavior; avoiding temptation.	The addict continues to visit recovery meetings to gain support and reinforcement against relapse.

Screening Recommendations

Tables 2.4-4 and 2.4-5 outline recommended health care screening measures by gender and age.

TABLE 2.4-4. Health Screening Recommendations for Women by Age

	Recommendation		
Age in Years	**Cardiovascular**	**Breast/Reproductive**	**Other**
19–39	BP screening at least once every 2 years. Cholesterol screening starting at age 20 for patients at ↑ risk of heart disease.	Pap test every 3 years starting at age 21; co-testing (Pap + HPV) may be done every 5 years starting at age 30. Chlamydia test yearly until age 24 if sexually active. Women ≥ 25 should be tested only if there is an ↑ risk. HIV test at least once to ascertain status. Test for gonorrhea and syphilis if at increased risk.	**Diabetes:** Blood glucose or HbA_{1c} screening starting if BP > 135/80 mm Hg or taking medication for hypertension.
40–49	BP screening at least once every 2 years. Cholesterol screening for patients at increased risk of heart disease.	Pap test every 3 years or co-testing every 5 years. Pelvic examination yearly; chlamydia test if the patient has new or multiple partners. HIV test at least once to ascertain status. Test for gonorrhea and syphilis if at increased risk.	**Diabetes:** Blood glucose or HbA_{1c} screening starting if BP > 135/80 mm Hg or taking medication for hypertension.
50–64	BP screening at least once every 2 years. Cholesterol screening for patients at increased risk of heart disease.	Mammogram once every 1–2 years (can start at age 40, if patient chooses). Pap test every 3 years. Chlamydia test if the patient has new or multiple partners. HIV test at least once to ascertain status. Test for gonorrhea and syphilis if at increased risk.	**Diabetes:** Blood glucose or HbA_{1c} screening starting if BP > 135/80 mm Hg or taking medication for hypertension. **Bone:** Discuss BMD test with physician or nurse. **Colorectal:** FOBT yearly; flexible sigmoidoscopy every 5 years or colonoscopy every 10 years.
≥ 65	BP screening at least once every 2 years. Cholesterol screening for patients at increased risk of heart disease.	Mammogram once every 1–2 years until the age of 75. Discuss Pap test with physician or nurse. Chlamydia test if the patient has new or multiple partners. Discuss HIV test with physician or nurse. Test for gonorrhea and syphilis if at increased risk.	**Diabetes:** Blood glucose or HbA_{1c} screening starting if blood pressure higher than 135/80 or taking medication for hypertension. **Bone:** BMD test at least once. **Colorectal:** Screening with fecal occult blood testing, sigmoidoscopy, or colonoscopy until 75 years old.

Adapted with permission from the US Department of Health and Human Services, Washington, DC, http://www.womenshealth.gov/publications/our-publications/screening-tests-for-women.pdf.

TABLE 2.4-5. Health Screening Recommendations for Men by Age

	Recommendation		
Age in Years	Cardiovascular	Reproductive	Other
19–39	BP screening at least once every 2 years. Cholesterol screening starting at age 20 for patients at increased risk of heart disease. Screen all men above the age of 35.	Both partners should be tested for STDs, including HIV, before initiating sexual intercourse. Test for syphilis if at increased risk.	N/A
40–49	BP screening at least once every 2 years. Cholesterol screening for all men over the age of 35.	Discuss DRE and PSA with physician or nurse. HIV test at least once to ascertain status. Test for syphilis if at increased risk.	**Diabetes:** Blood glucose or HbA_{1c} screening starting if BP > 135/80 mm Hg or taking medication for hypertension.
50–64	BP screening at least once every 2 years. Cholesterol screening for all men over the age of 35.	Discuss DRE and PSA with physician or nurse. HIV test at least once to ascertain status. Test for syphilis if at increased risk.	**Diabetes:** Blood glucose or HbA_{1c} screening starting if BP > 135/80 mm Hg or taking medication for hypertension. **Colorectal:** FOBT yearly; flexible sigmoidoscopy every 5 years or colonoscopy every 10 years.
≥ 65	BP screening at least once every 2 years. Cholesterol screening for all men over the age of 35.	Discuss DRE and PSA with physician or nurse. Discuss HIV test with physician. Test for syphilis if at increased risk.	**Diabetes:** Blood glucose or HbA_{1c} screening starting if BP > 135/80 mm Hg or taking medication for hypertension. **Colorectal:** FOBT; flexible sigmoidoscopy every 5 years or colonoscopy every 10 years (patients > 75 should discuss with physician). **Abdominal aortic aneurysm:** One-time screening for men who have ever smoked.

Adapted with permission from the US Department of Health and Human Services, Washington, DC, http://www.womenshealth.gov/publications/our-publications/screening-tests-for-men.pdf.

Causes of Death

The leading cause of cancer mortality in the United States is lung cancer. Prostate and breast cancers are the most prevalent cancers in men and women, respectively, with lung and colorectal cancers ranking second and third most common in both sexes. Table 2.4-6 lists the principal causes of death in the United States by age group.

Q

A hypothetical study finds a ⊕ association between poor sleep habits and the risk of Parkinson disease. The RR is 10 and the p-value is 0.4. How do you interpret these results?

TABLE 2.4-6. Leading Causes of Death by Gender

Rank	Men	Women
1	Heart disease (24.6%)	Heart disease (22.9%)
2	Cancer (24.1%)	Cancer (21.8%)
3	Unintentional injuries (6.3%)	Stroke (6.1%)
4	Chronic lower respiratory diseases (5.4%)	Chronic lower respiratory diseases (6.0%)
5	Stroke (4.2%)	Alzheimer disease (4.7%)
6	Diabetes (3.1%)	Unintentional injuries (3.7%)
7	Suicide (2.5%)	Diabetes (2.8%)
8	Alzheimer disease (2.0%)	Influenza and pneumonia (2.3%
9	Influenza and pneumonia (2.0%	Kidney disease (1.8%)
10	Kidney disease (1.8%)	Septicemia (1.5%)

Adapted with permission from the Centers for Disease Control and Prevention, Atlanta, GA, http://www.cdc.gov/women/lcod/2011/WomenAll_2011.pdf. Data from 2011.

Reportable Diseases

By law, disease reporting is mandated at the state level, and the list of diseases that must be reported to public health authorities varies slightly by state. The CDC has a list of nationally notifiable diseases that states voluntarily report to the CDC. These diseases include but are not limited to those listed in Table 2.4-7.

TABLE 2.4-7. Common Reportable Diseases

Disease Category	Examples
STDs	HIV, AIDS, syphilis, gonorrhea, chlamydia, chancroid, HCV.
Tick-borne disease	Lyme disease, ehrlichiosis, Rocky Mountain spotted fever.
Potential bioweapons	Anthrax, smallpox, plague.
Vaccine-preventable disease	Diphtheria, tetanus, pertussis, measles, mumps, rubella, polio, varicella, HAV, HBV, H influenza (invasive), meningococcal disease.
Water-/food-borne disease	Cholera, giardiasis, Legionella, listeriosis, botulism, shigellosis, shiga toxin–producing Ecoli, salmonellosis, trichinellosis, typhoid.
Zoonoses	Tularemia, psittacosis, brucellosis, rabies.
Miscellaneous	TB, leprosy, toxic shock syndrome, SARS, West Nile virus, VRSA, coccidioidomycosis, cryptosporidiosis. MRSA is reportable in several states.

A

There is **not** sufficient evidence to reject the null hypothesis, and therefore there is insufficient evidence to support an association between poor sleep habits and the risk of Parkinson disease. Remember that the null hypothesis always assumes that there is no association between the exposure and outcome variables. If the p-value is > 0.05, then you cannot reject the null hypothesis.

HIGH-YIELD FACTS IN

ETHICS AND LEGAL ISSUES

General Principles 126

Informed Consent 126

Minors 126

Competence and Decision-Making Capacity 127

End-of-Life Issues 128

- Written Advance Directives 128
- Withdrawal of Care 128
- Euthanasia and Physician-Assisted Suicide 128
- Futile Treatment 128

Disclosure 129

- Full Disclosure 129
- Medical Errors 129
- Clinical Research 129

Confidentiality 129

Conflict of Interest 130

Malpractice 130

KEY FACT

In some cases (eg, psychiatric illness, grave disability), patients can be hospitalized against their will if they are deemed a threat to themselves or to others.

MNEMONIC

BRAIN of informed consent—

Benefit
Risks
Alternatives
Indications
Nature

KEY FACT

Patients with psychiatric illness can give consent if their decision-making capacity is intact.

MNEMONIC

In the absence of a living will or durable power of attorney for health care—

The SPOUSE CHIPS in For the patient

SPOUSE
CHIldren
Parent
Sibling
Friend (in this order)

KEY FACT

Ethics committees or **court orders** can be helpful when the patient lacks capacity, has no proxy or advance directives, and there is disagreement among family members, or when there is disagreement between the family and health care providers (ie, in cases of medical futility, parental refusal of necessary treatment for minors).

General Principles

- **Respect for autonomy:** Clinicians are obligated to respect patients as individuals and to honor their preferences.
- **Beneficence:** Physicians have a responsibility to act in the patient's best interest. Respect for patient autonomy may conflict with beneficence. In general, if a patient is mentally competent, respect for patient autonomy supersedes beneficence even if the physician believes the patient is not acting in his/her best interest.
  - **Example:** The physician has a responsibility to recommend a life-saving transfusion to a Jehovah's Witness **(beneficence)** and respect the patient's **autonomy** if he/she should refuse.
- **Nonmaleficence:** "Do no harm." All medical interventions involve benefits and risks, and physicians should generally only recommend treatments where the likely benefits outweigh the known risks.
  - **Example:** A surgeon declines to perform a procedure, because she thinks the patient will die intraoperatively.
- **Justice:** Health care is a scarce resource. Fairness and equality in distribution and delivery of health care are ongoing challenges for health policy and in the clinical arena.

Informed Consent

- Defined as willing and voluntary acceptance of a medical intervention by a patient after adequate discussion with a physician about the **nature** of the intervention along with its **indications, risks, benefits,** and potential **alternatives** (including no treatment).
- **Patients may change their minds at any time.**
- Informed consent is required for significant procedures unless:
  - Emergency treatment is required.
    - **Examples:** An unconscious patient presents with cerebral edema after a motor vehicle collision, or a patient without previously indicated DNR/DNI (do not resuscitate/do not intubate) status undergoes cardiac arrest.
  - Patient lacks decision-making capacity (consent is still required but must be obtained from a surrogate decision maker). When possible, assent should be obtained from the patient lacking capacity.
    - **Examples:** Patients may present with dementia or significant psychiatric disturbances. Minors generally require surrogate decision makers until they demonstrate adequate decision-making capacity or are of legal age.

Minors

In general, minors (persons < 18 years of age) cannot consent for their own medical treatment and require parents or guardians to consent on their behalf, except in the following situations:

- **Life-threatening emergencies** when parents cannot be contacted.
- **Legal emancipation:** Emancipated minors do not require parental con-

sent for medical care. Although emancipation laws vary from state to state, in general minors are emancipated if they are married, are in the armed services, or are financially independent of their parents and have obtained legal emancipation.

- **Sexually transmitted infections and substance abuse treatment:** Rules concerning contraception, pregnancy, and abortion services and treatment for drug and alcohol dependency vary across the United States. In some states the physician is left with the decision of informing parents about adolescent use of confidential services in the interest of best serving the patient; other states limit disclosure.
- **Refusal of treatment:** A parent has the right to refuse treatment for his/her child as long as those decisions do not pose a serious threat to the child's well-being (eg, refusing immunizations is not considered a serious threat). If a parental decision is not in the best interest of the child, a physician may provide treatment against parental wishes. In emergent situations, if withholding treatment jeopardizes the child's safety, treatment can be initiated on the basis of legal precedent.
  - **Example:** A physician provides blood transfusion to save the life of a 6-year-old child seriously injured in a motor vehicle collision despite parental requests to withhold such a measure.

Competence and Decision-Making Capacity

- **Competence:** A person's **global and legal capacity to make decisions** and be held accountable in a court of law. **Competence is assessed by the courts** and is distinct from the term **decision-making capacity.**
- **Decision-making capacity:** The ability of a patient to understand relevant information, appreciate the severity of the medical situation and its consequences, communicate a choice, and deliberate rationally about his/her values in relation to the decision being made. This can be **assessed by the physician.**
- Decision-making capacity is best understood as varying with the complexity of the decision involved.
  - **Example:** The level of capacity needed for a decision about liver transplantation is different from that needed to choose between two types of pain medication for fracture-related pain.
- Incompetent patients, as assessed by the courts, or temporarily incapacitated patients may still be able to provide assent for treatment or refuse treatment. However, the need to treat supersedes the refusal of an incapacitated patient in emergency situations.
  - **Example:** An extremely hypertensive patient with altered mental status who refuses treatment must receive antihypertensive therapy, as this constitutes a medical emergency.
- In general, patients who have decision-making capacity have the right to refuse or discontinue treatment.
  - **Example:** Jehovah's Witnesses can refuse blood products.
- A patient's decision to refuse treatment can be overruled if the choice endangers the health and welfare of others.
  - **Example:** A patient with active TB must undergo antibiotic treatment, because not treating would pose a public health threat.

Q 1

A 47-year-old man is diagnosed with pancreatic cancer. His diagnosis and treatment options are discussed, but the patient refuses any intervention. He states that he would like to go home to his wife and children to die peacefully. What is the most appropriate next step in management?

Q 2

A 5-year-old girl with hydrocephalus needs another revision of her ventriculoperitoneal shunt. There are no satisfactory alternatives available to relieve her symptoms. Her father consents, but her mother refuses, arguing that she has been through enough procedures in her young life. What is the most appropriate next step in management?

Q 3

A 51-year-old man is brought to the ED after he was struck by a motor vehicle. He is unresponsive and in need of emergent surgery. His wife and children cannot be reached. What is the most appropriate next step in treatment?

End-of-Life Issues

WRITTEN ADVANCE DIRECTIVES

- **Living will:** Addresses a patient's wishes to maintain, withhold, or withdraw life-sustaining treatment in the event of terminal disease or a persistent vegetative state when the patient has lost the capacity to make decisions. **DNR** and **DNI** orders are based on patient preferences regarding CPR and intubation only. Patients can refuse all nonpalliative treatments or specific therapies (CPR, intubation, antibiotics, feeding tubes, etc).
- **Durable power of attorney for health care:** Legally designates a surrogate health care decision maker if a patient lacks decision-making capacity. **More flexible than a living will.** Surrogates should make decisions consistent with the person's stated wishes.
- If no living will or durable power of attorney for health care exists, decisions should be made by close family members (spouse, adult children, parents, and adult siblings) or friends, in that order.

KEY FACT

DNR/DNI orders do **not** mean "do not treat."

KEY FACT

Brain death is the irreversible loss of all brain activity and is equivalent to cardiopulmonary death. If a patient is brain dead, no consent is needed to stop therapy.

WITHDRAWAL OF CARE

- Patients and their decision makers have the right to forego or withdraw life-sustaining treatment. Nevertheless, physicians should seek to understand patients and their reasons for refusing beneficial treatments.
- No ethical distinction is made between **withholding** a treatment and **withdrawing** a treatment, because a patient may choose to refuse an intervention either **before** or **after** it is initiated. This can include ventilation, fluids, nutrition, and medications such as antibiotics.
- If the intent is to relieve suffering and medications administered are titrated for that purpose, it is considered ethical to provide palliative treatment to relieve pain and suffering even if it may hasten a patient's death **(principle of double effect).**
  - **Example:** A physician may prescribe an ↑ dose of an opioid analgesic to a patient who is expected to die within a day, even though it may suppress respiration and hasten death.

1 **A**

Respectfully ask the patient about his reasons for not wanting to pursue treatment. Patients often need clarification and reassurance. If he continues to decline treatment, you should abide by his decision **(respect for autonomy).**

EUTHANASIA AND PHYSICIAN-ASSISTED SUICIDE

- **Euthanasia** is the administration of a lethal agent with the intent to end life.
  - It is opposed by the AMA Code of Medical Ethics and is **illegal in all states.**
  - Patients who request euthanasia should be evaluated for inadequate pain control and comorbid depression.
- **Physician-assisted suicide** consists of prescribing a lethal agent to a patient who will self-administer it to end his/her own life. This is currently illegal except in the states of Oregon, Washington, Montana, Vermont, and New Mexico. Though legal in the aforementioned states, according to the AMA Code of Medical Ethics, physician-assisted suicide is "fundamentally incompatible with the physician's role as healer."

2 **A**

Proceed with the shunt revision. The **consent of one parent is sufficient** to proceed with the treatment of a minor, particularly when it is unequivocally clear that the decision is in the child's best interest.

3 **A**

Proceed with the surgery. A physician may give emergent treatment in the absence of informed consent when immediate intervention is necessary to prevent serious harm or death.

FUTILE TREATMENT

Physicians are not ethically obligated to provide treatment and may refuse a patient's or family member's request for further intervention on the grounds of futility under any of the following circumstances:

- There is no evidence or pathophysiologic rationale for the treatment.
- The intervention has already failed.
- Maximal intervention is currently failing.
- Treatment will not achieve the goals of care.

Disclosure

FULL DISCLOSURE

- Patients have a right to know about their medical status, prognosis, and treatment options (full disclosure). They have the legal right to obtain copies of their medical records.
- A patient's family cannot require that a physician withhold information from the patient without the knowledge and consent of the patient.
- A physician may withhold information only if the patient requests not to be told, or in the rare and controversial case in which a physician determines that disclosure would cause severe and immediate harm to the patient **(therapeutic privilege).**

MEDICAL ERRORS

- Physicians are **obligated** to inform patients of mistakes made in their medical treatment.
- If the cause of a specific error or series of errors is not known, the physician should communicate this with the family promptly and maintain contact with the patient as investigations reveal more facts.

CLINICAL RESEARCH

- Physicians are obligated to inform patients considering involvement in a clinical research protocol about the purpose of the research study and the entire study design as it will affect the patient's treatment. This includes the possible risks, benefits, and alternatives to the research protocol.
- An informed consent form approved by the overseeing research institutional review board must be completed for participation in any clinical research protocol.

Confidentialit

- Information disclosed by a patient to his/her physician and information about a patient's medical condition are confidential and should be discussed and accessed only by those directly involved in the patient's care, with few exceptions (described below).
- A patient may waive the obligation of the physician to protect confidentiality (eg, with insurance companies, authorized family members), preferably by way of written consent.
- It is ethically and legally necessary to override confidentiality in the following situations:
  - **Patient intent to commit a violent crime (**Tarasoff **decision):** Physicians have a **duty to protect** the intended victim through reasonable means (eg, warn the victim, notify police).
  - Suicidal patients.

KEY FACT

Potential signs of elder mistreatment:

- Cuts, bruises, pressure ulcers, burns
- Uncommon fractures
- Malnutrition or dehydration
- Anogenital injury or infection
- Evidence of poor caretaking or financial exploitation

KEY FACT

Signs of suspected child abuse:

- History given not consistent with injury
- Delay in seeking medical care
- Subdural hematomas
- Retinal hemorrhages
- Spiral, bucket-handle, or rib fractures
- Injuries in different stages of healing
- Unusual child or parental behavior

MNEMONIC

Overriding confidentiali y—

WAIT a SEC before letting a dangerous patient go!

Wounds
Automobile-driving impairment
Infectious disease
Tarasoff—violent crimes
Suicide
Elder mistreatment
Child abuse

Q

A 35-year-old woman visits a primary care physician after hurting her wrist. Physical examination reveals circumferential bruises of her wrist, neck, and arms. The patient admits that the injuries were inflicted by her husband. What is the most appropriate next step in management?

KEY FACT

Mandatory reporting of intimate-partner violence is controversial and varies by state. Nonetheless, physicians should document the encounter, offer support, and have resources available for assistance.

KEY FACT

Guiding principles for overriding confidentiality:

- There is an identifiable third party at risk for harm.
- The harm is significant and probable.
- Disclosure will help prevent or mitigate the harm.
- Other measures, such as convincing the patient to self-disclose, have failed.

KEY FACT

Physicians are not obligated to accept everyone coming to them as a patient. Furthermore, physicians have the right to end a doctor-patient relationship but must give the patient the resources and time to find another physician.

MNEMONIC

The 4 D's of malpractice—

Duty
Dereliction
Damage
Direct cause

A

Offer support and acknowledge the courage it takes to discuss abuse. Assess the safety of the woman and of any children involved, introduce the concept of an emergency plan, and encourage the use of community resources. If the patient consents, report the abuse to relevant authorities.

- Child abuse/neglect and elder mistreatment.
- Reportable infectious diseases (eg, HIV, sexually transmitted infections, tuberculosis). Duty to warn public officials and identifiable people at risk. It is normally best to encourage patients themselves to inform loved ones who are at risk for contracting the illness.
- Gunshot and knife wounds (duty to notify the police).
- The patient is a danger to others (eg, impaired automobile drivers). Currently, only six states have mandatory physician reporting laws.
  - **Example:** A patient begins to drive 1 week after hospitalization for seizures, although the department of motor vehicles in his state requires that licensed drivers be without seizures for at least 3 months.

Conflict of Interest

- Occurs when physicians find themselves having a personal interest in a given situation that influences their professional obligations.
  - **Example:** A physician may own stock in a pharmaceutical company (financial interest) that produces a drug he is prescribing to his patient (patient care interest).
- Physicians should disclose existing conflicts of interest to affected parties (eg, patients, institutions, audiences of journal articles or scientific meetings).

Malpractice

The essential elements of a civil suit under negligence include the **4 D's:**

- The physician has a **Duty** to the patient.
- **Dereliction** of duty occurs.
- There is **Damage** to the patient.
- Dereliction is the **Direct** cause of damage.

Unlike a criminal suit, in which the burden of proof is "beyond a reasonable doubt," the burden of proof in a malpractice suit is "a preponderance of the evidence."

HIGH-YIELD FACTS IN

GASTROINTESTINAL

Esophageal Disease 132
- Dysphagia/Odynophagia 132
- Infectious Esophagitis 133
- Diffuse (Distal) Esophageal Spasm 133
- Achalasia 134
- Esophageal Diverticula 134
- Esophageal Cancer 134
- Gastroesophageal Reflux Disease 135
- Hiatal Hernia 136

Disorders of the Stomach and Duodenum 137
- Gastritis 137
- Gastric Cancer 138
- Peptic Ulcer Disease 138
- Zollinger-Ellison Syndrome 139

Disorders of the Small Bowel 140
- Diarrhea 140
- Malabsorption/Maldigestion 142
- Lactose Intolerance 142
- Carcinoid Syndrome 142
- Irritable Bowel Syndrome 143
- Small Bowel Obstruction 143
- Ileus 144
- Mesenteric Ischemia 145
- Appendicitis 145

Disorders of the Large Bowel 146
- Diverticular Disease 146
- Large Bowel Obstruction 146
- Colorectal Cancer 146
- Ischemic Colitis 148

Gastrointestinal Bleeding 149

Inflammatory Bowel Disease 149

Hernias 150

Biliary Disease 150
- Cholelithiasis and Biliary Colic 150
- Acute Cholecystitis 153
- Choledocholithiasis 154
- Acute Cholangitis 154
- Gallstone Ileus 155

Liver Disease 155
- Abnormal Liver Function Tests 155
- Hepatitis 155
- Cirrhosis 159
- Primary Sclerosing Cholangitis 161
- Primary Biliary Cirrhosis 162
- Non-Alcoholic Fatty Liver Disease 162
- Hepatocellular Carcinoma 162
- Hemochromatosis 163
- Wilson Disease (Hepatolenticular Degeneration) 163

Pancreatic Disease 164
- Insulinoma 164
- VIPoma 164
- Pancreatitis 164
- Pancreatic Cancer 164

Esophageal Disease

DYSPHAGIA/ODYNOPHAGIA

KEY FACT

In an immunocompromised person with odynophagia, consider candidiasis.

Difficulty swallowing (dysphagia) or pain with swallowing (odynophagia) due to abnormalities of the oropharynx or esophagus.

History/Pe

Presentation of dysphagia varies according to location:

- **Oropharyngeal dysphagia:**
  - Problem with **initiation of swallowing,** may involve aspiration of food into the lungs, leading to coughing, choking, or drooling.
  - **Etiology:** Neurologic or muscular, including stroke, Parkinson disease, myasthenia gravis, prolonged intubation, and Zenker diverticula.
  - Usually more of a problem with **liquids than with solids.**
- **Esophageal dysphagia:**
  - Problem is with an **obstruction** (includes strictures, Schatzki rings, webs, carcinoma) or **motility disorder** (includes achalasia, scleroderma, esophageal spasm).
  - Obstructions usually more of a problem with **solids than with liquids;** while motility disorders cause both solid and liquid food dysphagia.
  - Examine for masses (eg, goiter, tumor) and anatomic defects.

KEY FACT

Esophageal webs are associated with iron deficiency anemia and glossitis (Plummer-Vinson syndrome).

Diagnosis

- **Oropharyngeal dysphagia:** Initially, modified barium swallow (video fluoroscopic swallowing exam). Occasionally esophagogastroduodenoscopy (EGD).



FIGURE 2.6-1. Oropharyngeal candidiasis. Multiple thick, yellowish-white plaques are seen on the palate and buccal mucosa. (Reproduced with permission from Kantarjian HM et al. MD Anderson Manual of Medical Oncology, 1st ed. New York, NY: McGraw-Hill; 2006.)

TABLE 2.6-1. Causes of Infectious Esophagitis

Etiologic Agent	Examfindings	Upper Endoscopy	Treatment
Candida albicans	± oral thrush (see Figure 2.6-1).	Yellow-white plaques adherent to the mucosa.	Fluconazole PO (treat with more than a topical agent alone).
Herpes simplex virus	Oral ulcers.	Small, deep ulcerations; multinucleated giant cells with intranuclear inclusions on biopsy + Tzanck smear.	Acyclovir IV.
Cytomegalovirus	Retinitis, colitis.	Large, superficial ulcerations; intranuclear and intracytoplasmic inclusions on biopsy.	Ganciclovir IV.

- **Esophageal dysphagia:** Initially, EGD. Consider pre-EGD barium swallow (aka esophagram) if history of esophageal radiation or strictures as these patients may be at higher risk of esophageal perforation. In any patient presenting with dysphagia, which most patients with esophageal disease have, **always perform EGD before moving on to secondary tests** as detailed in the individual diseases below. May be followed by manometry.
- **Odynophagia:** EGD.

Treatment

Etiology dependent. Treat the underlying disorder. Minimize food aspiration.

INFECTIOUS ESOPHAGITIS

Seen in **immunocompromised** patients. Table 2.6-1 outlines the etiology, diagnosis, and treatment of infectious esophagitis.

KEY FACT

Candidal esophagitis is an AIDS-defining illness.

DIFFUSE (DISTAL) ESOPHAGEAL SPASM

Motility disorder in which normal peristalsis is periodically interrupted by high-amplitude **nonperistaltic** contractions (see Figure 2.6-2A).

History/Pe

Presents with heartburn, chest pain, dysphagia, and odynophagia. **Often precipitated by ingestion of hot or cold liquids; relieved by nitroglycerin.**

Diagnosis

- EGD to rule out structural abnormalities (see Dysphagia section above).
- **Barium swallow: Corkscrew-shaped esophagus,** for very specific suspicion of DES.
- **Esophageal manometry (definitive test):** High-amplitude, simultaneous contractions in greater than 20% of swallows.

KEY FACT

The musculature of the upper third of the esophagus is skeletal, whereas that of the lower two-thirds is smooth muscle.

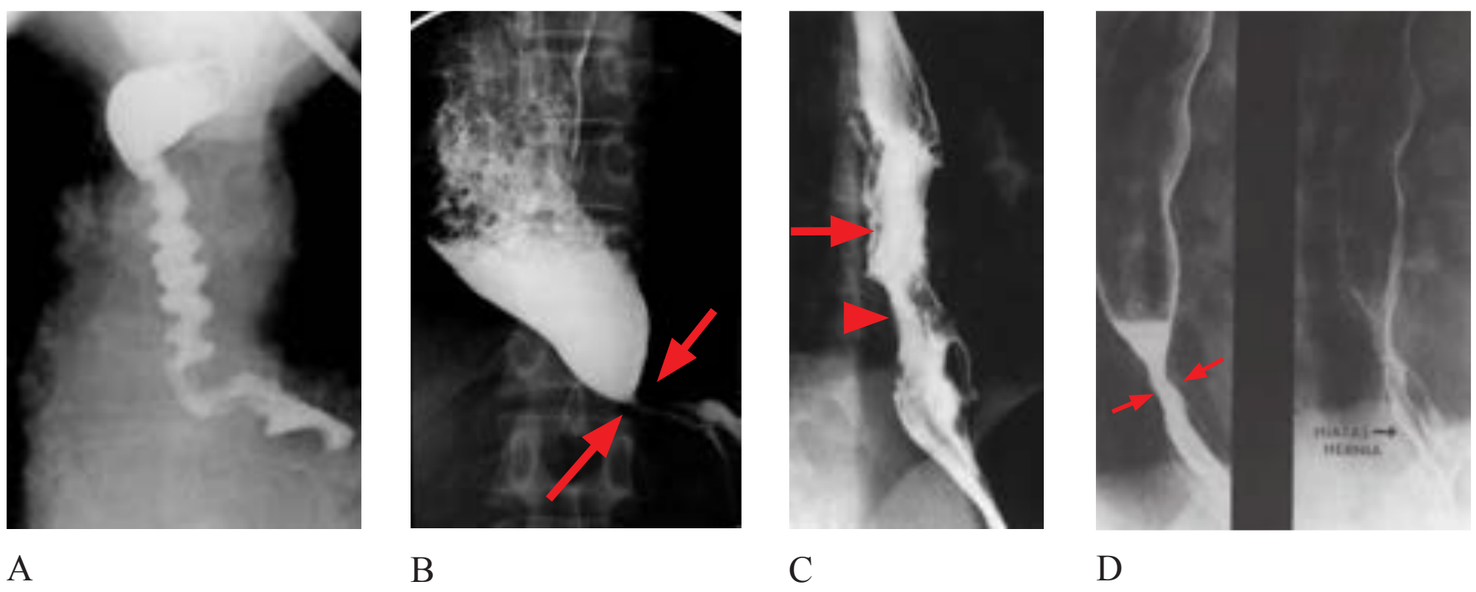


FIGURE 2.6-2. Esophageal disease on barium esophagram. (A) Esophageal spasm. (B) Achalasia. Note the dilated esophagus tapering to a "bird's beak" narrowing (arrows) at the LES. **(C) Barrett esophagus** with adenocarcinoma. Note the nodular mucosa of Barrett esophagus (arrow) and the raised filling defect (arrowhead) representing adenocarcinoma in this patient. **(D) Peptic stricture** (arrows) 2° to GERD above a hiatal hernia (right). (Image A reproduced with permission from USMLE-Rx.com. Image B reproduced with permission from Doherty GM. Current Diagnosis & Treatment: Surgery, 13th ed. New York, NY: McGraw-Hill; 2010. Images C and D reproduced with permission from Chen MY et al. Basic Radiology, 1st ed. New York, NY: McGraw-Hill; 2004.)

Treatment

- **Symptomatic relief:** Calcium channel blockers, tricyclic antidepressants (TCAs), or nitrates.
- **Severe, incapacitating symptoms:** Surgery (esophageal myotomy) but has limited utility.

ACHALASIA

- Motility disorder of the esophagus characterized by **impaired relaxation of the lower esophageal sphincter (LES)** and **loss of peristalsis** in the distal two-thirds of the esophagus.
- **Etiology:** Degeneration of the inhibitory neurons in the myenteric (Auerbach) plexus.

History/PE

Progressive dysphagia (solids and liquids), chest pain, regurgitation of undigested food, weight loss, and nocturnal cough.

KEY FACT

Beware: malignancy may mimic achalasia (pseudoachalasia).

Diagnosis

- EGD to rule out structural disorders beyond achalasia (ie, mechanical obstruction) that may present similarly to achalasia (pseudoachalasia), especially cancer.
- **Barium swallow (initial test):** Esophageal **dilation with a "bird's beak" tapering** of the distal esophagus (see Figure 2.6-2B).
- **Manometry (definitive test): ↑ resting LES pressure, incomplete LES relaxation** upon swallowing, and ↓ **peristalsis** in the body of the esophagus (see Figure 2.6-3).

Treatment

- **Short term:** Nitrates, calcium channel blockers, or endoscopic injection of botulinum toxin into the LES.
- **Long term:** Pneumatic balloon dilation or surgical (Heller) myotomy.

ESOPHAGEAL DIVERTICULA

- Diverticula can be present in any location. **Zenker diverticulum** is defined as cervical outpouching through the cricopharyngeus muscle and is a posterior, false diverticulum.
- **Hx/PE:** Chest pain, dysphagia, halitosis, and regurgitation of undigested food.
- **Dx:** Barium swallow will demonstrate outpouchings.
- **Tx:** If symptomatic, treat with surgical excision of the diverticulum. For Zenker diverticulum, **myotomy** of the cricopharyngeus is required to relieve the high-pressure zone.

ESOPHAGEAL CANCER

KEY FACT

Squamous cell esophageal cancer is associated with tobacco and alcohol use.

- **Most common worldwide: squamous cell carcinoma** (SCC).
- **Most common in United States, Europe, and Australia: Adenocarcinoma.**
- Risk factors include the following:
  - **SCC:** Alcohol, tobacco use, and nitrosamines.
  - **Adenocarcinoma:** Barrett esophagus (columnar metaplasia of the distal esophagus 2° to chronic GERD).

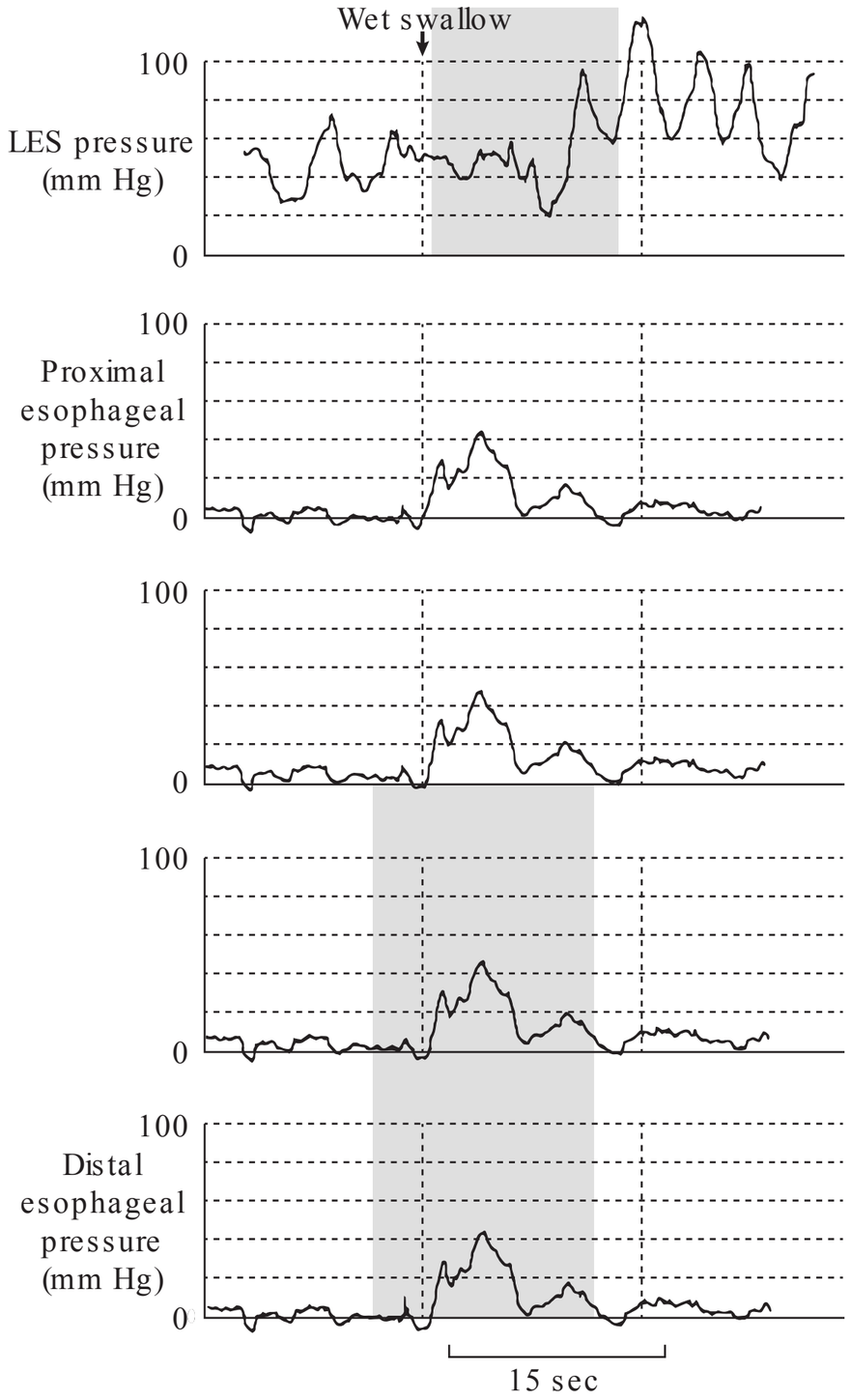


FIGURE 2.6-3. Achalasia. Manometry with incomplete LES relaxation. (Reproduced with permission from Farrokhi F, Vaezi MF. Idiopathic (primary) achalasia, Orphanet J Rare Dis 2007 Sep 26;2:38.)

History/Pe

Progressive dysphagia, initially to solids and later to liquids, is common. Weight loss, odynophagia, GERD, GI bleeding, and vomiting are also seen.

Diagnosis

- **Barium study (initial test):** Narrowing of esophagus with an irregular border protruding into the lumen (see Figure 2.6-2C).
- **EGD with biopsy:** Establishes the diagnosis.
- **CT and endoscopic ultrasound:** Staging.

Treatment

Chemoradiation and surgical resection are first-line treatment. Resection is also indicated in cases of high-grade Barrett dysplasia. Has a poor prognosis.

KEY FACT

Esophageal cancer metastasizes early, because the esophagus lacks a serosa.

KEY FACT

SCC of the esophagus tends to occur in the upper and middle thirds of the esophagus, whereas adenocarcinoma occurs in the lower third.

GASTROESOPHAGEAL REFLUX DISEASE

Symptomatic reflux of gastric contents into the esophagus, most commonly from **transient LES relaxation.** Can also result from an incompetent LES, gastroparesis, or hiatal hernia.

History/Pe

- **History: Heartburn** that commonly occurs 30–90 minutes **after a meal, worsens with reclining,** and often improves with antacids, sitting, or standing, sour taste ("water brash"), a globus sensation (a sensation of a lump in the throat), unexplained cough, morning hoarseness, and chest pain mimicking CAD.
- **Examination: Normal** unless systemic disease (eg, scleroderma) is present.

Diagnosis

- **Primarily a clinical diagnosis,** with empirical treatment first (see below for lifestyle modification and medical treatment).
- **EGD with biopsy:** Performed in patients whose symptoms are (1) refractory to initial empiric therapy, (2) long standing (to rule out Barrett esophagus and adenocarcinoma; see Figure 2.6-4), or (3) associated with **alarm symptoms** (eg, blood in the stool, weight loss, dysphagia/odynophagia, chest pain).
- **24-hour pH monitoring with impedance (definitive test):** Indicated if diagnosis is uncertain.
- **Other studies:** Indicated for refractory symptoms or if concern for other causes. May include barium swallow (may demonstrate reflux see Figure 2.6-2D) or esophageal manometry (see Figure 2.6-3).

KEY FACT

GERD can also mimic angina or MI.

KEY FACT

GERD is not a result of the presence of Helicobacter pylori. GERD arises from a transient relaxation of the LES.

Treatment

- **Lifestyle:** Weight loss, head-of-bed elevation, small but frequent meals, and avoidance of nocturnal meals and substances that ↓ LES tone (eg, avoid alcohol, chocolate, coffee).
- **Pharmacologic:**
  - **Mild/intermittent: Antacids.**
  - **Chronic/frequent: H_2 receptor antagonists** (cimetidine, ranitidine) or **PPIs** (omeprazole, lansoprazole).
  - Severe/erosive: PPIs first; if refractory, **Nissen fundoplication** surgery may be of benefit.
  - **Complications:** Erosive esophagitis, esophageal peptic stricture, aspiration pneumonia, upper GI bleeding, **Barrett esophagus.**

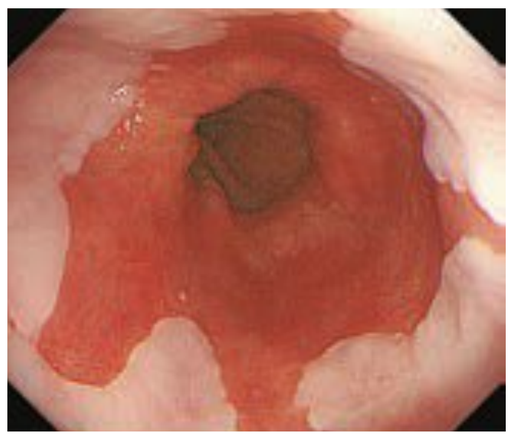


FIGURE 2.6-4. Barrett esophagus on upper endoscopy. Shown is an irregular Z line (squamocolumnar junction between the esophagus and stomach) due to columnar metaplasia of the lower esophagus. (Reproduced with permission from Fauci AS et al. Harrison's Principles of Internal Medicine, 17th ed. New York, NY: McGraw-Hill; 2008.)

HIATAL HERNIA

- Herniation of stomach upward into the chest through the diaphragm. Three common types:
  - **Sliding hiatal hernia (95%):** Gastroesophageal junction and a portion of the stomach are displaced above the diaphragm, usually asymptomatic (see Figure 2.6-5A).
  - **Paraesophageal hiatal hernia (5%):** Gastroesophageal junction remains below the diaphragm, while the fundus herniates into the thorax; can cause strangulation (see Figure 2.6-5B).
  - **Mixed hiatal hernias** (rare).
- **Hx/PE:** May be asymptomatic. Patients with sliding hernias may present with GERD.
- **Dx:** Incidental finding on CXR; also frequently diagnosed by barium swallow or EGD.
- **Tx:**
  - **Sliding hernias:** Medical therapy and lifestyle modifications to ↓ GERD symptoms.
  - **Paraesophageal hernias:** Surgical gastropexy (attachment of the stomach to the rectus sheath and closure of the hiatus) to prevent gastric volvulus.

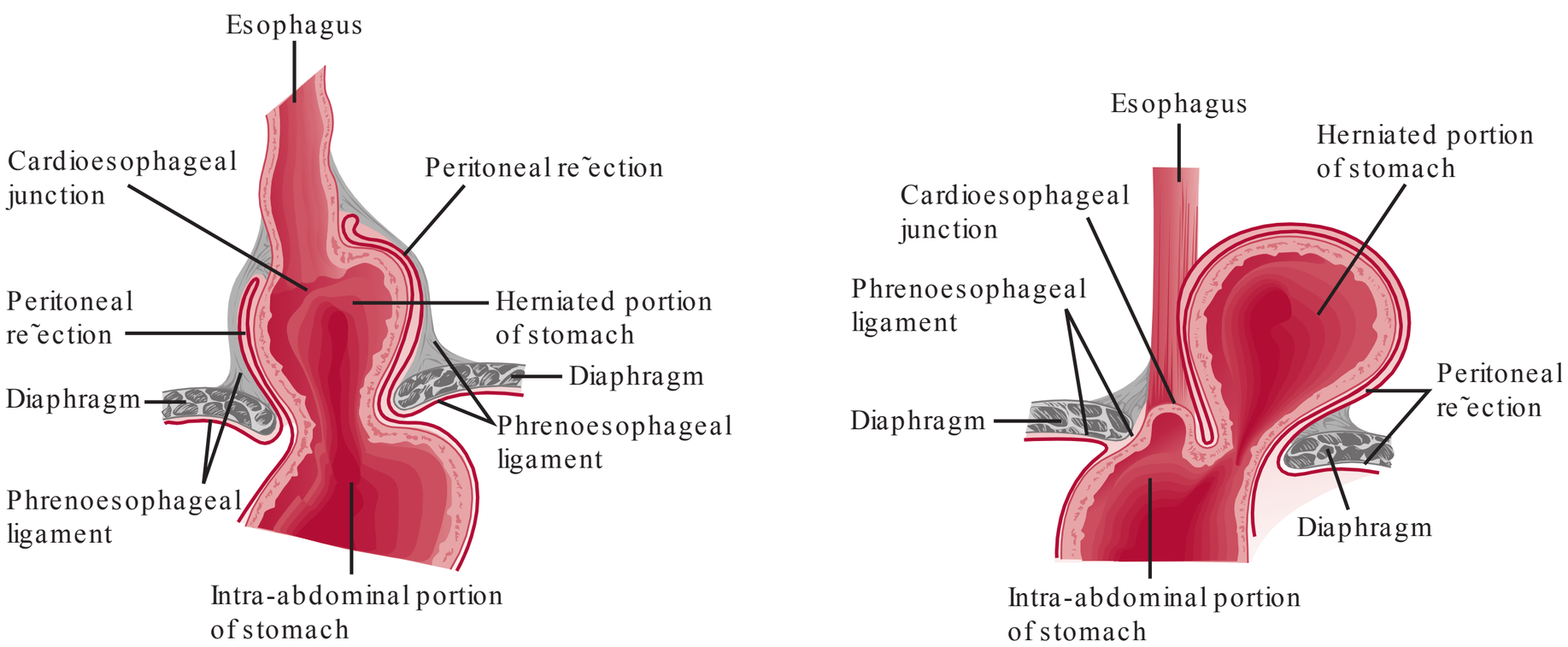


FIGURE 2.6-5. Hiatal hernia. (A) Sliding hiatal hernia. (B) Paraesophageal hiatal hernia. (Reproduced with permission from Doherty GM. Current Diagnosis & Treatment: Surgery, 13th ed. New York, NY: McGraw-Hill; 2010.)

Disorders of the Stomach and Duodenum

GASTRITIS

Inflammation of the gastric mucosa. Subtypes:

- **Acute gastritis:** Rapidly developing, superficial lesions, often due to **NSAID** use, alcohol, H pylori infection, and stress from severe illness (eg, burns, CNS injury).
- **Chronic gastritis:**
  - **Type A (10%):** Occurs in the fundus and is due to **autoantibodies to parietal cells.** Causes **pernicious anemia** and is associated with other autoimmune disorders and ↑ risk of gastric adenocarcinoma and carcinoid tumors.
  - **Type B (90%):** Occurs in the antrum and may be caused by NSAIDs or H pylori **infection.** Often asymptomatic, but associated with an ↑ risk of peptic ulcer disease (PUD) and gastric cancer. **Note:** H pylori **infection can but does not always cause gastritis.**

History/Pe

Asymptomatic or symptoms of epigastric pain, nausea, vomiting, hematemesis, or melena.

Diagnosis

See Table 2.6-2.

Treatment

- **Stop intake of exacerbating agents such as NSAIDs or alcohol.**
- Antacids, sucralfate, H_2 receptor blockers, and/or proton pump inhibitors (PPIs) may help.
- Administer triple therapy (amoxicillin, clarithromycin, omeprazole) to treat H pylori infection unless the patient is allergic to penicillin, in which case metronidazole should be substituted for amoxicillin.

KEY FACT

Type A gastritis is associated with pernicious anemia due to lack of intrinsic factor necessary for the absorption of vitamin B_{12}.

KEY FACT

Stress ulcers include Curling ulcers, which are associated with burn injuries, and Cushing ulcers, which are associated with traumatic brain injury.

KEY FACT

Hpylori antibodies stay ⊕ even when the infection is cleared. Use the urea breath test or a repeat stool antigen as a test of cure.

TABLE 2.6-2. Tests for H pylori

Test	Description	Test Characteristics
Serology	Detect IgG antibodies to H pylori.	High sensitivity, lower specificity (screening). Cannot distinguish between treated and active disease.
Urea breath test	H pylori urease converts urea to CO_2 and ammonia; this test detects ammonia formed from urea metabolism.	High specificity, lower sensitivity. PPIs may cause false negatives.
Stool antigen test	Detects H pylori antigens in stool.	High specificity, high sensitivity. Cost-effective initial test for H pylori.
Endoscopic biopsy	Detect H pylori on histology or culture. Can also detect intestinal metaplasia, MALT, or widespread gastritis.	Gold standard for diagnosis of gastritis and H pylori. Most invasive test.

- Give prophylactic PPIs to patients at risk for stress ulcers (eg, ICU patients).

KEY FACT

Consider peptic ulcer disease or gastritis in elderly patients who are taking medications for arthritis or heart disease (eg, NSAIDs) who present with abdominal pain or GI bleeding.

GASTRIC CANCER

- Malignant tumor (mostly adenocarcinoma) with a poor prognosis that is particularly common in Korea and Japan.
- **Risk factors:** Diet high in nitrites and salt and low in fresh vegetables (antioxidants), H pylori colonization, and chronic gastritis.
- **Hx/PE:** Early-stage disease is usually asymptomatic but may be associated with indigestion and loss of appetite. Late-stage disease presents with alarm symptoms: abdominal pain, weight loss, and upper GI bleeding.
- **Dx:** Upper endoscopy with biopsy (definitive test) to rule out other etiologies and confirm the diagnosis.
- **Tx:** If detected early, treatment is surgical resection. Most patients present with late-stage, incurable disease. Five-year survival is < 10% for advanced disease.

KEY FACT

A gastric adenocarcinoma that metastasizes to the ovary is called a Krukenberg tumor.

KEY FACT

MALT lymphoma is a rare gastric tumor that presents in patients with chronic H pylori infection. It is the only malignancy that can be cured with antibiotics. Treat with triple therapy.

PEPTIC ULCER DISEASE

- Results from damage to the gastric or duodenal mucosa caused by impaired mucosal defense and/or ↑ acidic gastric contents.
- **Risk factors:** H pylori (> 90% of duodenal ulcers and 70% of gastric ulcers), **NSAIDs, alcohol,** and **tobacco use;** concomitant use of corticosteroids and NSAIDs; **gender** (males > females).

History/PE

- **Presentation:** Chronic or periodic **dull, burning epigastric pain** that is often related to meals and can radiate to the back; nausea; hematemesis ("coffee-ground" emesis); or hematochezia (blood in the stool).
- **Examination:** Usually normal but may reveal **epigastric tenderness** and stool guaiac.
- **Risks:** Acute perforation (rigid abdomen, rebound tenderness, and/or guarding).

KEY FACT

Gastric cancer may present with Virchow node (an enlarged left supraclavicular lymph node).

Diagnosis

- If **suspect perforation,** perform upright KUB (see Figure 2.6-6) to evaluate air under the diaphragm or CT abdomen.
- **Upper endoscopy (definitive test)** with biopsy to confirm and to rule out active bleeding or gastric adenocarcinoma (10% of gastric ulcers without perforation).
- H pylori testing.
- In recurrent or refractory cases, check serum gastrin levels to screen for Zollinger-Ellison syndrome.

Treatment

- **Acute management:**
  - **If perforation suspected:** AXR (initial test) to rule out free air under the diaphragm. Consider CT (definitive test) if AXR shows no perforation but there is high clinical suspicion. Then, surgery if perforation is confirmed on CT. Carefully monitor BP.
  - **Rule out active bleeding:** Serial hematocrits (initially), rectal vault examination, NG lavage. Monitor BP and treat with IV hydration, blood transfusion, and IV PPIs. Then, perform an urgent EGD (definite) to control suspected bleeding.
- **Long-term management:**
  - **Medical therapy goals:** Protect the mucosa, ↓ acid production, and eradicate H pylori infection.
    - **Mild disease:** Treat with antacids, PPIs, or H_2 blockers.
    - H pylori **infection:** Triple therapy (omeprazole, clarithromycin, and amoxicillin).
    - Discontinue exacerbating agents (alcohol, tobacco).
- **Endoscopy with targeted biopsy:** Indicated in patients with symptoms refractory to medical therapy to rule out gastric cancer.
- **Surgical therapy (eg, parietal cell vagotomy):** Severe cases refractory to medical therapy.

Complications

Hemorrhage (most likely from posterior ulcers that erode into the gastroduodenal artery), gastric outlet obstruction, perforation, intractable pain.

ZOLLINGER-ELLISON SYNDROME

- Rare condition characterized by **gastrin-producing tumors** in the duodenum and/or pancreas that lead to oversecretion of gastrin.
- Oversecretion of gastrin leads to ↑ gastric acid production and recurrent or intractable **ulcers.**
- In 20% of cases, gastrinomas are associated with multiple endocrine neoplasia (MEN) type 1.
- **Hx/PE:** Unresponsive, recurrent **gnawing, burning abdominal pain** as well as with **diarrhea,** nausea, vomiting, fatigue, weakness, weight loss, and **GI bleeding.**
- **Dx: ↑ fasting serum gastrin levels** and ↑ **gastrin with the administration of secretin** are diagnostic; CT is indicated to characterize and stage disease.
- **Tx:**
  - **Control symptoms:** Moderate- to high-dose PPIs.
  - Surgical resection of the gastrinoma after localization by CT or octreotide scan to identify suspected carcinoid tumors.

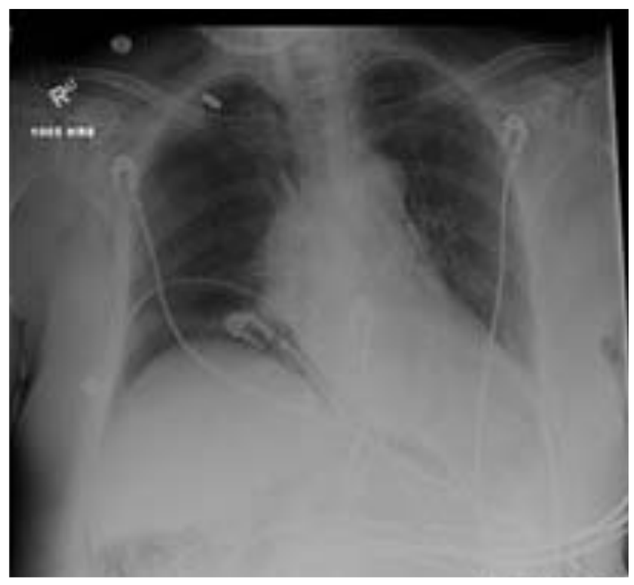


FIGURE 2.6-6. Pneumoperitoneum. Upright CXR reveals free air under the diaphragm. (Reproduced with permission from USMLE-Rx.com.)

KEY FACT

After a meal, pain from a **G**astric ulcer is **G**reater, whereas **D**uodenal pain **D**ecreases.

KEY FACT

All gastric ulcers must be biopsied to rule out malignancy.

KEY FACT

Misoprostol can help patients with PUD who require NSAID therapy (eg, for arthritis).

KEY FACT

Zollinger-Ellison syndrome:
- Hypercalcemia (MEN type 1).
- Epigastric pain (peptic ulcer).
- Diarrhea (due to mucosal damage and pancreatic enzyme inactivation leading to malabsorption).

Disorders of the Small Bowel

DIARRHEA

KEY FACT

Cryptosporidium and Isospora are associated with chronic diarrhea in patients with HIV/AIDS.

- The production of > **200 g of feces per day along with ↑ frequency or ↑ liquidity of stool.** The most common mechanisms are malabsorption/maldigestive/osmotic, secretory, inflammatory/infectious, and ↑ motility (see also Tables 2.6-3 and 2.6-4).
- **Stool electrolytes:** Primarily sodium and potassium (normal stool osmotic gap is 50–100 mOsm/kg).

$$\text{Stool osmotic gap} = 290 - 2 * (\text{stool Na} + \text{stool K})$$

History/Pe

KEY FACT

Organisms that cause bloody diarrhea include Salmonella, Shigella, Ecoli (EHEC), and Campylobacter.

- **Acute diarrhea:** Acute onset with a duration of < 2 weeks; usually infectious and self-limited.
  - Multiple pathogens may be responsible (see Table 2.6-4).
  - Common causes of **pediatric diarrhea** are **Rotavirus, Norwalk virus, and enterovirus infection.**
- **Chronic diarrhea:** Insidious onset with a duration of > 4 weeks.
  - **Secretory:** Carcinoid tumors, VIPomas.
  - **Malabsorption/maldigestive/osmotic:** Bacterial overgrowth, pancreatic insufficiency, mucosal damage, lactose intolerance, celiac disease, laxative abuse, postsurgical short bowel syndrome.
  - **Inflammatory/infectious:** IBD.
  - **Increased motility:** Irritable bowel syndrome (IBS).

Diagnosis

KEY FACT

Organisms that cause watery diarrhea include Vibrio cholerae, rotavirus, Ecoli (ETEC), Cryptosporidium, Giardia, and Norovirus.

- **Acute diarrhea:** No further studies are indicated unless the patient has a high fever, bloody diarrhea, or diarrhea lasting > 4–5 days.
- **Chronic diarrhea:** History/physical examination to narrow the differential diagnosis. Additional studies include the following:
  - **Stool analysis:** Leukocytes, culture, C difficile toxin, and ova and parasite exam (O&P).
  - **Sigmoidoscopy:** Uncommonly done, but useful in patients with bloody diarrhea with no obvious clinical suspicion.

TABLE 2.6-3. Types of Stool Osmotic Gap

Stool osmotic gap	description	examples
Low osmotic gap (< 50 mOsm/kg)	Secretory diarrhea: ↑ secretion or inhibition of absorption of water.	Bacterial toxins (eg, cholera, Escherichia coli), VIPoma, gastrinoma, medullary cancer of thyroid.
High osmotic gap (>100 mOsm/kg)	Osmotic diarrhea: osmotically active compounds in bowel draw in water.	Celiac disease, Whipple disease, pancreatic insufficie y, laxative abuse.

TABLE 2.6-4. Causes of Infectious Diarrhea

Infectious agent	History	Exam and test results (note: all have fecal RBCs and WBCs)	Comments	Treatment
Campylobacter	**The most common etiology of bacterial diarrhea.** Caused by ingestion of contaminated food or water. Affects young children and young adults; generally lasts 7–10 days.	Frequently presents with bloody diarrhea.	Rule out appendicitis and IBD.	Supportive treatment first, then fluoroquinolones (eg, ciprofloxacin) or azithromycin.
Clostridium difficile	Associated with recent treatment with antibiotics (penicillins, quinolones, **clindamycin**). Affects hospitalized adult patients. **Watch for toxic megacolon (seen on AXR).**	Presents with fever, abdominal pain, and possible systemic toxicity.	Most commonly causes colitis, but can involve the small bowel. Identify C difficile toxin in the stool. Sigmoidoscopy shows pseudomembranes.	**Cessation of the inciting antibiotic.** Treat with PO metronidazole (mild disease), PO vancomycin (moderate-severe disease), or IV metronidazole ± rectal vancomycin (if ileus).
Entamoeba histolytica	Caused by ingestion of contaminated food or water; look for a history of travel in developing countries. The incubation period can last up to 3 months.	Presents with severe abdominal pain and fever. Endoscopy shows "flask-shaped" ulcers.	Chronic amebic colitis mimics IBD.	Steroids can lead to fatal perforation. Treat with metronidazole.
Ecoli O157:H7	Caused by ingestion of contaminated food (raw meat). Affects children and the elderly; generally lasts 5–10 days.	Presents with severe abdominal pain, low-grade fever, and vomiting.	It is important to rule out GI bleeding and ischemic colitis. HUS is a potential complication, primarily in children.	Avoid antibiotic or antidiarrheal therapy, which ↑ HUS risk.
Salmonella	Caused by ingestion of contaminated poultry or eggs. Affects young children and the elderly; generally lasts 2–5 days.	Presents with a prodromal headache, fever, myalgia, and abdominal pain.	Sepsis is a concern, as 5–10% of patients become bacteremic. Sickle cell patients are susceptible to invasive disease leading to osteomyelitis.	First fluids. Treat bacteremia or at-risk patients (eg, sickle cell patients) with oral quinolone or TMP-SMX.
Shigella	Extremely contagious; transmitted between people by the fecal-oral route. Affects young children and institutionalized patients.		May lead to severe dehydration. Can also cause febrile seizures in the very young.	Treat with TMP-SMX to ↓ person-to-person spread.

Treatment

- **Acute diarrhea:**
  - **Oral rehydration** is key.
  - Antibiotics are not indicated (except in C difficile infection, or in the epidemic setting), because they don't shorten the course of illness.
  - **Treatment of symptoms:** Antidiarrheal agents (eg, loperamide, bismuth salicylate). Avoid if the patient has high fever or bloody stools.
- **Chronic diarrhea:** Treatment is etiology specific.

KEY FACT

Diarrhea after ingestion of raw eggs or dairy: think Salmonella.

MALABSORPTION/MALDIGESTION

KEY FACT

The initial tests specific for celiac disease are IgA anti-transglutaminase antibody or antiendomysial antibody. The gold standard is intestinal biopsy.

- Inability to absorb macro- and/or micronutrients. Common etiologies include the following:
  - **Mucosal abnormalities:** Celiac disease (associated with dermatitis herpetiformis; see Figure 2.6-7), Whipple disease, tropical sprue.
  - **Bile salt deficiency:** Ileal disease in Crohn disease or small bowel resections (> 100 cm of terminal ileum), bacterial overgrowth.
  - **Other:** Pancreatic insufficiency, short bowel syndrome.
- **Hx/PE:** Presents with **frequent, loose, watery stools** (carbohydrate malabsorption) and/or **pale, foul-smelling, bulky stools** (steatorrhea or fat maldigestion) associated with abdominal pain, **flatus, bloating,** weight loss, **nutritional deficiencies,** and fatigue.
- **Dx:** Multiple laboratory tests based on the clinical suspicion. Biopsy is definitive.
- **Tx:** Etiology dependent. In severe cases, patients may require TPN, immunosuppressants, and anti-inflammatory medications.



FIGURE 2.6-7. Dermatitis herpetiformis. Grouped, papulovesicular, pruritic skin lesions are shown. Lesions tend to be symmetrically located on the extensor surfaces of the elbows, knees, buttocks, and posterior scalp, and are associated with celiac disease. (Reproduced with permission from Caproni M et al. Celiac Disease and Dermatologic Manifestations: Many Skin Clue to Unfold Gluten-Sensitive Enteropathy. Gastroenterol Res Pract. 2012;2012:952753.)

LACTOSE INTOLERANCE

- Results from a **deficiency of lactase,** a brush-border enzyme that hydrolyzes lactose into glucose and galactose.
- Common among populations of African, Asian, and Native American descent, also transiently after an acute episode of gastroenteritis.
- **Hx/PE:** Presents with **abdominal bloating, flatulence, cramping,** and **watery diarrhea following milk ingestion.**
- **Dx:** Often treated empirically with lactose-free diet. **Hydrogen breath test** reveals ↑ hydrogen following the ingestion of lactose.
- **Tx:** Avoidance of dairy products; oral lactase enzyme replacement.

KEY FACT

Patients with carcinoid syndrome also develop niacin deficiency because tryptophan is metabolized into serotonin.

CARCINOID SYNDROME

- Due to the metastasis of **carcinoid tumors,** which most commonly arise from the ileum and appendix and produce serotonin. Prior to metastasis, most secreted hormones undergo first-pass metabolism by the liver and do not cause systemic symptoms.
- **Hx/PE: Cutaneous flushing, diarrhea, abdominal cramps, wheezing,** and right-sided **cardiac valvular lesions** are the most common manifestations.
- **Dx:** High urine levels (initial test) of the serotonin metabolite 5-HIAA are diagnostic. CT and In-111 octreotide scans are used to localize the tumor.
- **Tx:** Treatment includes **octreotide** and surgical resection.

KEY FACT

The classic presentation of pellagra is the **4 D's: D**iarrhea, **D**ementia, **D**ermatitis, and **D**eath.

IRRITABLE BOWEL SYNDROME

- An idiopathic functional disorder characterized by chronic, intermittent abdominal pain and changes in bowel habits.
- **Epidemiology:** Women in their 20s to 30s (though affects both genders of all ages), often patients have comorbid psychiatric disorders (eg, depression, anxiety, fibromyalgia).

History/Pe

- Patients present with abdominal pain that is relieved by bowel movements, diarrhea and/or constipation, abdominal distention, and mucous stools. Symptoms often worsen with stress.
- **No alarm symptoms:** Rarely awakens patients from sleep; vomiting, significant weight loss, and constitutional symptoms are uncommon.
- **Examination:** Usually unremarkable.

Diagnosis

- **Definition (per Rome III diagnostic criteria):** At least 3 days in 3 months of episodic abdominal discomfort that is (two or more criteria): (1) relieved by defecation; (2) associated with a change in stool frequency or consistency; (3) associated with a change in stool appearance.
- Exclude **organic disorders** such as IBD using tests like CBC, TSH, electrolytes, stool cultures, abdominal films, barium contrast studies, and, colonoscopy with biopsy.
- Increased incidence of celiac disease in IBS, so celiac should be ruled out when suspect IBS.

Treatment

- **Psychosocial:** Patients benefit from a strong patient-physician relationship. Physicians should offer reassurance and should not dismiss the symptoms.
- **Diet: Fiber supplements** (psyllium); exclude gas-producing foods.
- **Pharmacologic:** Symptomatic treatment with antispasmodics. TCAs and SSRIs may help. Long-term medical therapy is usually not indicated.

SMALL BOWEL OBSTRUCTION

- Defined as partial or complete blockage of passage of bowel contents through the small bowel.
- **Etiologies: Adhesions** from prior abdominal surgery (60% of cases), **hernias** (10–20%), neoplasms (10–20%), intussusception, gallstone ileus, stricture due to IBD, and volvulus.
- **Partial SBO:** Continued passage of flatus, but no stool.
- **Complete SBO:** No passage of flatus or stool (obstipation).

History/Pe

- **Hx:** Crampy abdominal pain at 4- to 5-minute intervals; **vomiting** typically follows the pain.
- **Abdominal examination:** Distention, tenderness, prior surgical scars, or hernias, hyperactive bowel sounds (**high-pitched tinkles** and **peristaltic rushes**).
- **Complications:** Ischemic necrosis and bowel rupture with prolonged or complete obstruction. Patients present with peritonitis manifested by fever, hypotension, rebound tenderness, and tachycardia.

KEY FACT

In the United States, the leading cause of SBO in children is hernia. The leading cause of SBO in adults is adhesions.

Q

A 53-year-old woman with a history of carcinoid tumor of the appendix (status post resection) presents to a local clinic with symmetric, dry, hyperpigmented skin lesions and persistent diarrhea. Her husband expresses concern that the patient does not seem to be herself anymore; he reports that she has been irritable, confused, and forgetful. What is the most likely diagnosis?

KEY FACT

Gallstone ileus is a form of SBO that occurs when a gallstone lodges at the ileocecal valve.

Diagnosis

- Abdominal films (initial test) demonstrate a **stepladder pattern of dilated small bowel loops, air-fluid levels** (see Figure 2.6-8), and a paucity of gas in the colon.
- CT of the abdomen (definitive test) to further characterize obstruction and evaluate for etiology.
- CBC may demonstrate **leukocytosis** if there is ischemia or necrosis of bowel.
- Lab tests often reveal **dehydration** and **metabolic alkalosis.** Lactic acidosis is a prognostic sign, as it suggests necrotic bowel.

Treatment

- **Initial management:** Fluid resuscitation.
- **Partial obstruction:** Supportive care may be sufficient and should include NPO status, NG suction, IV hydration, correction of electrolyte abnormalities, and Foley catheterization to monitor fluid status, pain management; avoid opioids and anticholinergics (slow GI motility).
- **Complete obstruction:** Exploratory laparotomy indicated in complete SBO, ischemic necrosis, or refractory SBO symptoms.

ILEUS

- Loss of peristalsis without structural obstruction.
- **Risk factors:** Recent surgery/GI procedures, severe medical illness, immobility, hypokalemia or other electrolyte imbalances, hypothyroidism, diabetes mellitus (DM), and medications that slow GI motility (eg, anticholinergics, opioids).

History/Pe

- **History:** Diffuse, constant abdominal discomfort, **nausea and vomiting,** and an **absence of flatus or bowel movements.**
- **Examination:** Diffuse tenderness, **abdominal distention,** and ↓ **or absent bowel sounds; rectal examination required** to rule out fecal impaction in elderly patients.

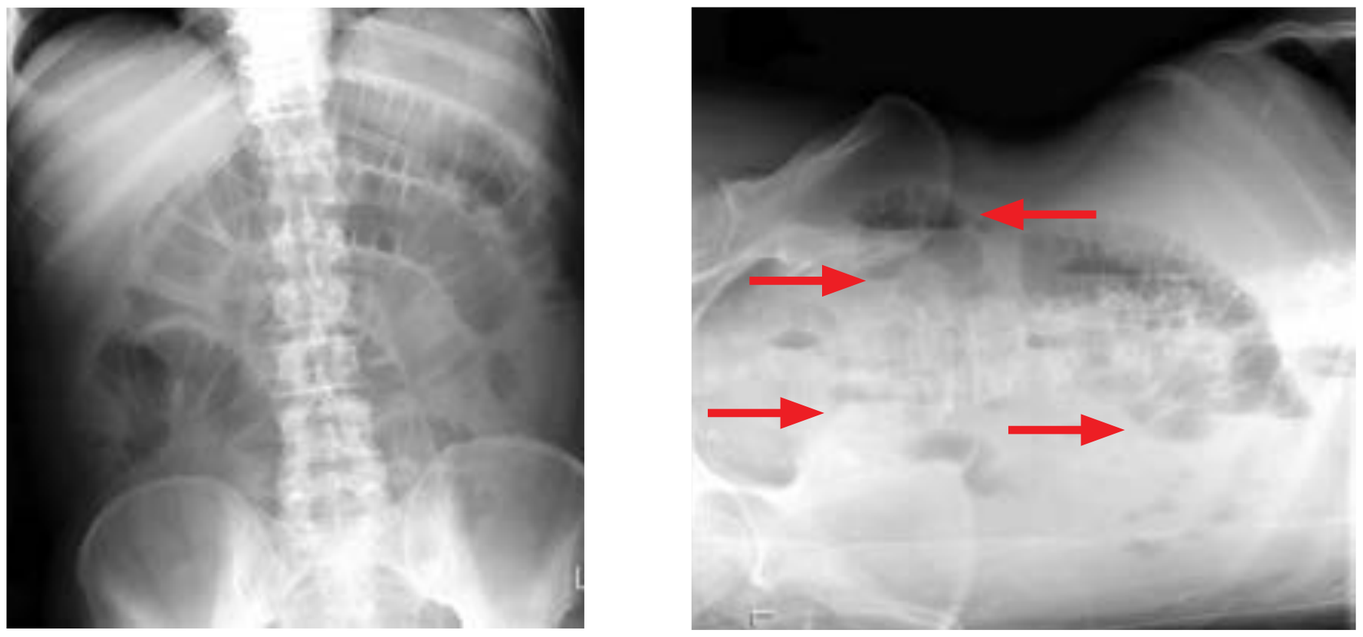


FIGURE 2.6-8. Small bowel obstruction. (A) Supine abdominal radiograph shows dilated air-filled small bowel loops with relatively little gas in the colon. **(B)** Left lateral decubitus radiograph on the same patient demonstrates multiple air-fluid levels (arrows) at different levels. These are typical plain film findings of complete SBO. (Reproduced with permission from Doherty GM. Current Diagnosis & Treatment: Surgery, 13th ed. New York, NY: McGraw-Hill; 2010.)

A

Pellagra, a deficiency of vitamin B_3 (niacin), 2° to a recurrent carcinoid tumor. Carcinoid tumors produce serotonin, which is a derivative of tryptophan. However, tryptophan is also the precursor of niacin. In patients with carcinoid tumors, the tumor can be so active that most tryptophan is used for serotonin production, resulting in niacin deficiency.

Diagnosis

- Must consider clinical history in diagnosis.
- **Abdominal films (initial): Distended loops of small and large bowel,** with air seen throughout the colon and rectum (SBO has no air distal to the obstruction).
- CT of the abdomen is the definitive test.

Treatment

- ↓ or discontinue the use of narcotics and any other drugs that reduce **bowel motility.**
- **Bowel rest:** Temporarily ↓ or discontinue oral feeds.
- **Bowel decompression:** Initiate **NG suction/parenteral feeds** as necessary.
- **Supportive care:** Replete electrolytes as needed; hydrate with IV fluids.

KEY FACT

In ileus, there is air present throughout the small and large bowel on AXR.

MESENTERIC ISCHEMIA

Insufficient blood supply to the small intestine, resulting in ischemia and, potentially, necrosis. The most common causes are as follows:

- **Embolism:** Emboli most commonly originate in the heart. Risk factors include atrial fibrillation and stasis from a ↓ ejection fraction.
- **Acute arterial occlusion from thrombosis:** Most commonly occurs in the proximal SMA. The 1° risk factor is atherosclerosis.
- **Other causes:** Nonocclusive arterial disease (atherosclerosis of mesenteric vessels, arteriolar vasospasm), venous thrombosis (due to hypercoagulable states), or shock state.

History/Pe

Presents with **severe abdominal pain out of proportion to the examination,** nausea, vomiting, diarrhea, and bloody stools, prior episodes of abdominal pain after eating ("intestinal angina").

Diagnosis

- **AXR and CT:** May reveal bowel wall edema ("thumbprinting") and air within the bowel wall (pneumatosis intestinalis).
- **Mesenteric/CT angiography (definitive test):** Gold standard for diagnosis of arterial occlusive disease, but conventional angiography allows for intervention of thrombosis/embolism.

Treatment

- **For all:** Volume resuscitation, broad-spectrum antibiotics.
- **For acute arterial thrombosis or embolism:** Anticoagulation and either laparotomy or angioplasty.
- **For venous thrombosis:** Anticoagulation.
- **Surgery:** Resect infarcted bowel.

Complications

Sepsis/septic shock, multisystem organ failure, death.

APPENDICITIS

See the Emergency Medicine chapter.

Disorders of the Large Bowel

DIVERTICULAR DISEASE

KEY FACT

Diverticulosis is the most common cause of acute lower GI bleeding in patients > 40 years of age.

- **Diverticula: Outpouching** of mucosa and submucosa (false diverticula) that herniate through the colonic muscle layers in areas of high intraluminal pressure; most commonly found in the sigmoid colon.
- **Diverticulosis:** Many diverticula, **most common cause of acute lower GI bleeding** in patients > 40 years of age.
- **Diverticulitis:** Inflammation and, generally, micro-perforation of a diverticulum 2° to fecalith impaction.
- **Risk factors: Low-fiber and high-fat diet,** advanced age (65% occur in those > 80 years of age), and connective tissue disorders.

History/Pe

- **Diverticulosis:** Often **asymptomatic** until patients present with sudden, intermittent, painless bleeding, which can cause symptoms of anemia (fatigue, lightheadedness, dyspnea on exertion) when bleeding is severe.
- **Diverticulitis: LLQ abdominal pain, fever,** nausea, and vomiting. Perforation is a serious complication that presents with peritonitis and shock.

Diagnosis

KEY FACT

Sigmoidoscopy should be avoided in the initial stages of diverticulitis in light of the risk of perforation.

- Clinical history is important to diagnosis.
- CBC may show **leukocytosis** or anemia.
- In diverticulitis, CT scan (used to diagnose) may reveal inflammation or abscess (see Figure 2.6-9).
- Colonoscopy provides the definitive diagnosis in diverticular disease, however, **avoid sigmoidoscopy/colonoscopy in patients with acute diverticulitis** in view of the risk of perforation.

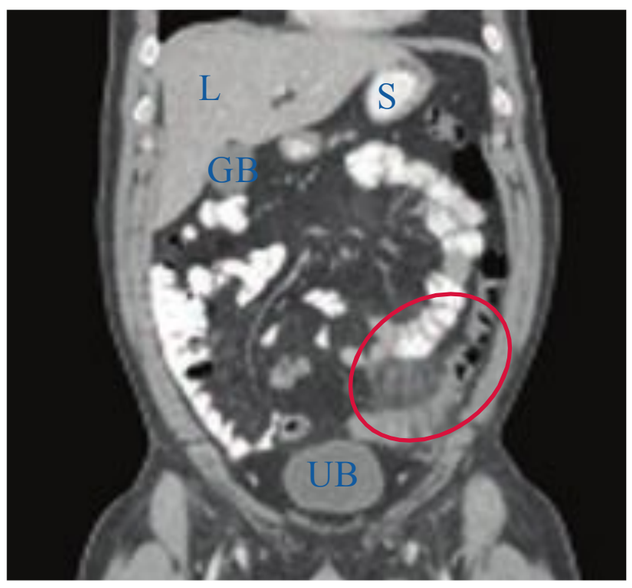


FIGURE 2.6-9. Acute diverticulitis. Coronal reconstruction from a contrast-enhanced CT demonstrates sigmoid diverticula with presigmoid inflammatory "fat stranding." The area of abnormality is circled in red. L = liver; S = stomach; GB = gallbladder; UB = urinary bladder. (Reproduced with permission from USMLE-Rx.com.)

Treatment

- **Uncomplicated diverticulosis:** Routine follow-up. Encourage a high-fiber diet or fiber supplements.
- **Diverticular bleeding:** Bleeding usually stops spontaneously; transfuse and hydrate as needed. If bleeding does not stop, hemostasis by colonoscopy, angiography with embolization, or **surgery** is indicated.
- **Diverticulitis:** Treat with **bowel rest** (NPO), NG tube placement (if severe), and **broad-spectrum antibiotics** (metronidazole and a fluoroquinolone or a second- or third-generation cephalosporin), colonoscopy after initial stage.
- **For perforation:** immediate surgical resection of diseased bowel via a Hartmann procedure with a temporary colostomy.

LARGE BOWEL OBSTRUCTION

Table 2.6-5 describes features that distinguish SBO from LBO. Figure 2.6-10 demonstrates the classic radiographic findings of LBO.

COLORECTAL CANCER

The second leading cause of cancer mortality in the United States. There is an ↑ incidence with age, with a peak incidence at 70–80 years. Risk factors and screening recommendations are summarized in Tables 2.6-6 and 2.6-7.

TABLE 2.6-5. Characteristics of Small and Large Bowel Obstruction

Variable	SBO	LBO
History	Moderate to severe acute abdominal pain; **copious emesis.** Cramping pain with distal SBO. Fever, signs of dehydration, and hypotension may be seen.	Constipation/obstipation, deep and cramping abdominal pain (less intense than SBO), nausea/vomiting (less than that of SBO, but more commonly **feculent**).
Exam	**Abdominal distention** (distal SBO), abdominal tenderness, visible peristaltic waves, fever, hypovolemia. Look for **surgical scars/hernias;** perform a rectal exam. **High-pitched "tinkly" bowel sounds;** later, absence of bowel sounds.	Significant **distention,** tympany, and tenderness; examine for peritoneal irritation or mass. Fever or signs of shock suggest perforation/peritonitis or ischemia/necrosis. **High-pitched "tinkly" bowel sounds;** later, absence of bowel sounds.
Etiologies	**Adhesions** (postsurgery), **hernias,** neoplasm, volvulus, intussusception, gallstone ileus, foreign body, Crohn disease, cystic fibrosis (CF), stricture, hematoma.	**Colon cancer,** diverticulitis, volvulus, fecal impaction, benign tumors. **Assume colon cancer until proven otherwise.**
Differential	LBO, paralytic ileus, gastroenteritis.	SBO, paralytic ileus, appendicitis, IBD, Ogilvie syndrome (pseudo-obstruction).
Diagnosis	CBC, electrolytes, lactic acid, AXR (see Figure 2.6-8); contrast studies (determine if it is partial or complete), CT scan.	CBC, electrolytes, lactic acid, AXR (see Figure 2.6-10), CT scan; water contrast enema (if perforation is suspected); sigmoidoscopy/colonoscopy if stable.
Treatment	Hospitalize. Partial SBO can be treated conservatively with **NG decompression** and NPO status. Patients with complete SBO should be managed aggressively with NPO status, NG decompression, IV fluid, electrolyte replacement, and **surgical correction.**	Hospitalize. Obstruction can be relieved with a Gastrografin enema, colonoscopy, or a **rectal tube;** however, **surgery** is usually required. Ischemic colon usually requires partial colectomy with a diverting colostomy. Treat the underlying cause (eg, neoplasm).

History/Pe

Most patients are asymptomatic. When they are symptomatic, symptoms depend on the location of the lesion:

- **Right-sided lesions:** Often bulky, ulcerating masses that lead to **anemia from chronic occult blood loss.** Patients may complain of weight loss, anorexia, diarrhea, weakness, or vague abdominal pain. Obstruction is rare. (Right colon has a larger diameter than left colon.)
- **Left-sided lesions:** Typically **"apple-core" obstructing** masses (see Figure 2.6-11). Patients complain of **obstruction, change in bowel habits** (eg, ↓ stool caliber, constipation, obstipation), and/or blood-streaked stools. (Left side has smaller diameter and thus is easier to obstruct.)
- **Rectal lesions:** Usually present with bright-red blood per rectum, often with tenesmus and/or rectal pain. Rectal cancer must be ruled out in all patients with rectal bleeding.

Diagnosis

- **Definitive diagnosis:** Colonoscopy with biopsy.
- **Evaluate for metastases:** CXR, LFTs, and an abdominal/pelvic CT.
- Staging is based on the depth of tumor penetration into the bowel wall and the presence of lymph node involvement and distant metastases.

KEY FACT

Iron deficiency anemia in an elderly patient indicates colorectal cancer until proven otherwise.

Q

A 60-year-old man with no past medical history presents with fever, dyspnea, and orthopnea of 2 weeks' duration. Physical examination reveals splinter hemorrhages and a new IV/VI diastolic decrescendo murmur. Echocardiogram confirms aortic valve endocarditis, and IV antibiotics are started. Blood cultures are ⊕ for Streptococcus bovis. What is the next diagnostic step?

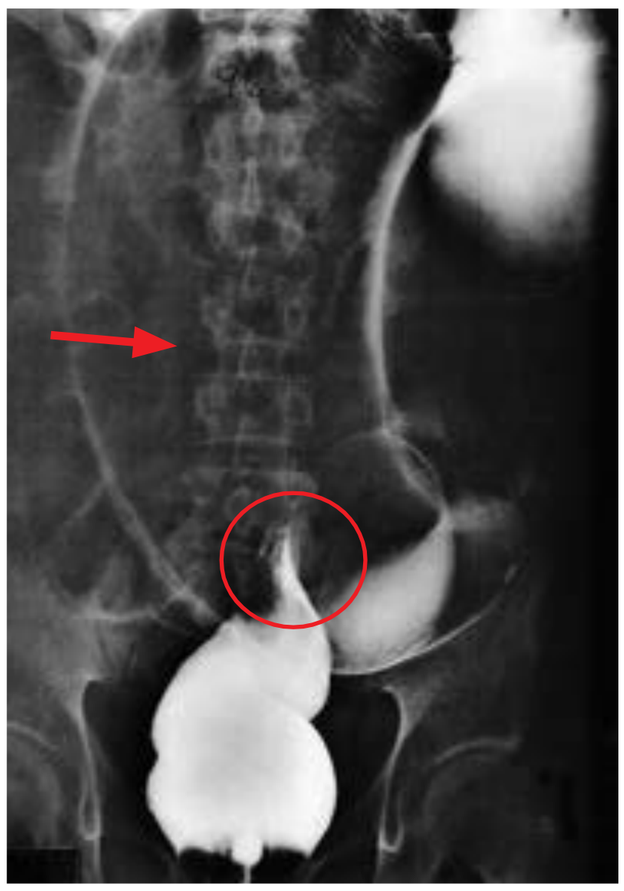


FIGURE 2.6-10. Large bowel obstruction. AP radiograph from a barium enema in a patient with an LBO reveals a massively dilated sigmoid colon (arrow) and a "bird's beak" appearance of the barium column at the site of volvulus (circle). (Reproduced with permission from Doherty GM. Current Diagnosis & Treatment: Surgery, 13th ed. New York, NY: McGraw-Hill; 2010.)

TABLE 2.6-6. Risk Factors for Colorectal Cancer

Risk Factor	Comments
Age	Risk ↑ with age; peak incidence is at 70–80 years.
Hereditary polyposis syndromes	Familial adenomatous polyposis (FAP; 100% risk by age 40); hereditary nonpolyposis colorectal cancer (HNPCC).
⊕ family history	Especially first-degree relatives < 60 years of age.
IBD	Ulcerative colitis > Crohn disease.
Adenomatous polyps	Villous > tubular; sessile > pedunculated.
High-fat, low-fiber diet	—

Treatment

- Surgical resection of the tumor is first-line treatment.
- **Adjuvant chemotherapy** is appropriate in cases with ⊕ lymph nodes.
- Follow with serial CEA levels to detect recurrence, colonoscopy, LFTs, CXR, and abdominal CT to screen for metastases.

ISCHEMIC COLITIS

- Insufficient blood supply to the colon that results in ischemia and, potentially, necrosis. Most commonly affects the left colon, particularly the "watershed area" at the splenic flexure. Usually occurs in the setting of atherosclerosis.
- **Hx/PE:** Presents with crampy **lower abdominal pain** followed by **bloody diarrhea** after meals or exertion or in the heat. Fever and peritoneal signs suggest bowel necrosis.
- **Dx:**
  - **CT scan with contrast (initial test):** Thickened bowel wall, atherosclerosis.
  - **Colonoscopy:** Pale mucosa with petechial bleeding.

TABLE 2.6-7. Screening Recommendations for Colorectal Cancer

Risk Category	Recommendations
No past medical or family history	Starting at age 50: ■ Annual DRE and home FOBT ■ Colonoscopy every 10 years **or** ■ Sigmoidoscopy every 5 years.
First-degree relative with colon cancer	Colonoscopy every 5 years starting at age 40 **or** Colonoscopy every 5 years starting 10 years prior to the age of the affected family member at the time of diagnosis (whichever comes first)
Ulcerative colitis	Colonoscopy every 1–2 years starting 8–10 years after diagnosis.

A

Colonoscopy. Although the mechanism of association has yet to be determined, there is a well-established association between Sbovis and colon cancer.

- **Tx:**
  - Supportive therapy with bowel rest, IV fluids, and broad-spectrum antibiotics.
  - Surgical bowel resection is indicated for infarction, fulminant colitis, or obstruction.

Gastrointestinal Bleeding

- GI bleeding presents as hematemesis, hematochezia, and/or melena.
- **Upper GI tract bleeding:** Bleeding from lesions proximal to the ligament of Treitz (the anatomic boundary between the duodenum and jejunum). Table 2.6-8 presents the features of upper and lower GI bleeding.

Inflammatory Bowel Diseas

Includes **Crohn disease** (see Figure 2.6-12) and **ulcerative colitis** (see Figure 2.6-13). Most common in Caucasians and **Ashkenazi Jews,** with onset most frequently occurring in the teens to early 30s or in the 50s. Table 2.6-9 summarizes the features of IBD. In patients with a history of Crohn disease and acute abdominal pain, suspect an SBO, which is due to the fistula formation. Ulcerative colitis does not cause fistulas.

KEY FACT

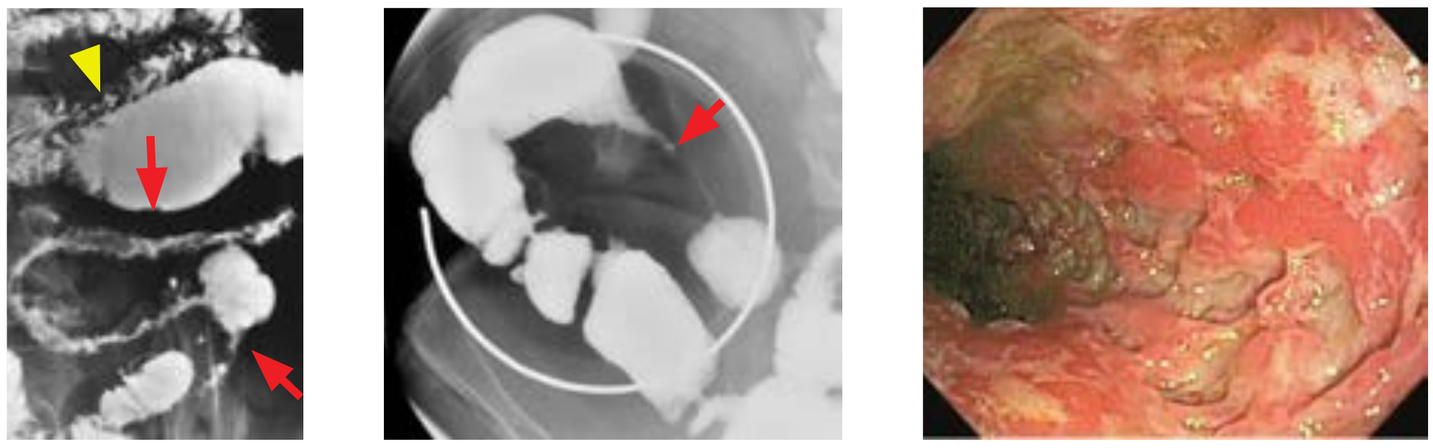
One unit of packed RBCs should ↑ hemoglobin by 1 g/dL and hematocrit by 3–4 units.



FIGURE 2.6-11. Colon carcinoma. The encircling carcinoma appears as an "apple-core" filling defect in the descending colon on barium enema x-ray. (Reproduced with permission from Way LW. Current Surgical Diagnosis & Treatment, 10th ed. Stamford, CT: Appleton & Lange; 1994.)

TABLE 2.6-8. Features of Upper and Lower GI Bleeding

Variable	Upper GI bleeding	Lower GI bleeding
History/exam	Hematemesis ("coffee-ground" emesis), melena > hematochezia, hypovolemia (eg, tachycardia, lightheadedness, hypotension).	Hematochezia > melena, but can be either.
Diagnosis	NG tube and lavage (may be ⊖ in 15% of upper GI bleeds); endoscopy is definitive.	Rule out upper GI hemorrhage with NG lavage if brisk. Anoscopy/sigmoidoscopy for patients < 45 years of age with small-volume bleeding. Colonoscopy if stable; arteriography or exploratory laparotomy if unstable.
Etiologies	**PUD,** esophagitis/gastritis, Mallory-Weiss tear, esophageal/gastric varices, gastric antral vascular ectasia, Dieulafoy lesions.	**Diverticulosis** (60%), angiodysplasia, IBD, hemorrhoids/fissures, neoplasm, AVM.
Initial management	Protect the airway (intubation may be needed). Stabilize the patient with IV fluids and packed RBCs (hematocrit may be normal early in acute blood loss).	Similar to that of upper GI hemorrhage.
Long-term management	Endoscopy followed by therapy directed at the underlying cause.	Depends on the underlying etiology. Endoscopic therapy (eg, epinephrine injection, cauterization or clip placement), intra-arterial vasopressin infusion or embolization, or surgery for diverticular disease or angiodysplasia.



A B C

FIGURE 2.6-12. Crohn disease. (A) Small bowel follow-through (SBFT) barium study shows skip areas of narrowed small bowel with nodular mucosa (arrows) and ulceration. Compare with normal small bowel (arrowhead). **(B)** Spot compression image from SBFT shows "string sign" narrowing (arrow) due to stricture. **(C)** Deep ulcers in the colon of a patient with Crohn disease, seen at colonoscopy. (Image A reproduced with permission from Chen MY et al. Basic Radiology, 1st ed. New York, NY: McGraw-Hill; 2004. Image B reproduced with permission from USMLE-Rx.com. Image C reproduced with permission from Fauci AS et al. Harrison's Principles of Internal Medicine, 17th ed. New York, NY: McGraw-Hill; 2008).

KEY FACT

Hesselbach triangle is an area bounded by the inguinal ligament, the inferior epigastric artery, and the rectus abdominis.

KEY FACT

MDs **D**on't **LIE.** Direct hernias lie **Me** **D**ial and indirect lie **L**ateral to the **I**nferior **E**pigastric vessels.

Hernias

Inguinal hernias are protrusions of abdominal contents (usually the small intestine) into the inguinal region through a weakness or defect in the abdominal wall. Classified as either direct or indirect. There are also **femoral hernias.** See Table 2.6-10 and Figure 2.6-14.

Treatment

Because of the risk of **incarceration** and **strangulation,** surgical correction is indicated.

Biliary Disease

CHOLELITHIASIS AND BILIARY COLIC

Colic results from transient cystic duct blockage from impacted stones. Although risk factors include the **four F's** (**F**emale, **F**at, **F**ertile, and **F**orty),



A B C

FIGURE 2.6-13. Ulcerative colitis. (A) Radiograph from a barium enema showing a featureless ("lead pipe") colon with small mucosal ulcerations (arrow). Compare with normal haustral markings in **(B). (C)** Diffuse mucosal ulcerations and exudates at colonoscopy in chronic ulcerative colitis. (Image A reproduced with permission from Doherty GM. Current Diagnosis & Treatment: Surgery, 13th ed. New York, NY: McGraw-Hill; 2010. Image B reproduced with permission from Chen MY et al. Basic Radiology. New York, NY: McGraw-Hill; 2004. Image C reproduced with permission from Fauci AS et al. Harrison's Principles of Internal Medicine, 17th ed. New York, NY: McGraw-Hill; 2008.)

TABLE 2.6-9. Features of Ulcerative Colitis and Crohn Disease

Variable	Ulcerative Colitis	Crohn Disease
Site of involvement	The **rectum** is always involved. May extend proximally in a **continuous fashion.** Inflamm tion and ulceration are **limited to the mucosa and submucosa.**	May involve **any portion** of the GI tract, particularly the **ileocecal region,** in a **discontinuous pattern** ("skip lesions"). The rectum is often spared. **Transmural inflamm tion** is seen, sometimes leading to fistulas o other organs.
History/exam	**Bloody diarrhea,** lower abdominal cramps, tenesmus, urgency. Examination may reveal orthostatic hypotension, tachycardia, abdominal tenderness, frank blood on rectal examination, and extraintestinal manifestations.	Abdominal pain, abdominal mass, low-grade fever, weight loss, watery diarrhea. Examination may reveal fever, abdominal tenderness or mass, **perianal fissu es or tags, fistula ,** and extraintestinal manifestations.
Extraintestinal manifestations	Aphthous stomatitis, episcleritis/uveitis, arthritis, **primary sclerosing cholangitis,** erythema nodosum, and pyoderma gangrenosum.	The same as ulcerative colitis in addition to fistulas o the skin, to the bladder, or between bowel loops.
Diagnosis	CBC, AXR, stool cultures, O&P, stool assay for C diffici . Colonoscopy can show diffuse and ontinuous rectal involvement, friability, edema, and **pseudopolyps.** Definiti e diagnosis can be made with biopsy.	The same lab workup as that of ulcerative colitis. Upper GI series with small bowel follow-through. Colonoscopy may show aphthoid, linear, or stellate ulcers, strictures, **"cobblestoning,"** and **"skip lesions."** "Creeping fat" may also be present during laparotomy. Definiti e diagnosis can be made with biopsy.
Treatment	**5-ASA agents** (eg, sulfasalazine, mesalamine), topical or oral; corticosteroids for fla e-ups and immunomodulators (eg, azathioprine) or biologics (eg, Infliximа) for refractory or moderate to severe disease. **Total proctocolectomy can be curative** for long-standing or fulminant colitis or **toxic megacolon;** also ↓ cancer risk.	**Similar to UC: 5-ASA agents;** corticosteroids for fla e-ups. May require immunomodulators (eg, azathioprine) or biologics (eg, Infliximа) for refractory or moderate to severe disease and for maintenance therapy. Surgical resection may be necessary for suspected perforation, stricture, fistula, or abs ess.
Incidence of cancer	There is a **markedly ↑ risk of colorectal cancer** in long-standing cases (monitor with frequent fecal occult blood screening and yearly colonoscopy with multiple biopsies after 8 years of disease).	The incidence of 2° malignancy is lower than that of ulcerative colitis but is greater than that of the general population.

TABLE 2.6-10. Types of Hernias

Hernia type	Location	Etiology	Prevalence
Indirect	Herniation of abdominal contents through both external and internal rings, lateral to inferior epigastric vessels (see Figure 2.6-14A).	Results from congenital patent processus vaginalis.	Most common.
Direct	Herniation through floor of Hesselbach t iangle, medial to epigastric vessels (see Figure 2.6-14B).	Mechanical breakdown in transversalis fascia resulting from age.	
Femoral	Herniation below inguinal ligament through femoral canal, below and lateral to the pubic tubercle.	Increased intra-abdominal pressure, weakened pelvic floo .	More common in women than men.

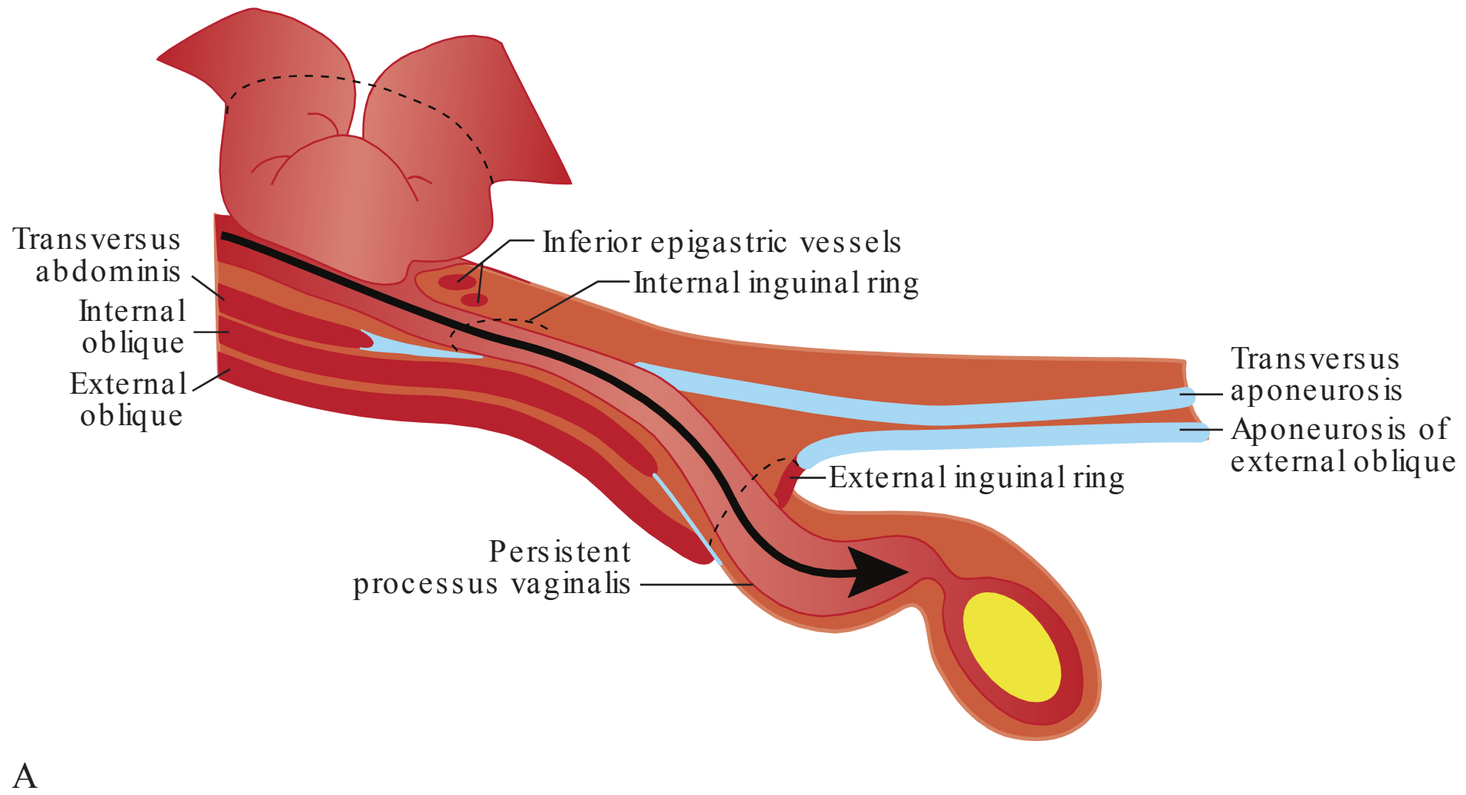


FIGURE 2.6-14. Indirect (A) and direct (B) inguinal hernias. (Reproduced with permission from Tintinalli JE et al. Tintinalli's Emergency Medicine: A Comprehensive Study Guide, 7th ed. New York, NY: McGraw-Hill; 2010.)

the disorder is common and can occur in any patient. Additional risk factors include OCP use, rapid weight loss, chronic hemolysis (pigment stones in sickle cell disease), small bowel resection (loss of enterohepatically circulated bile), and TPN. Table 2.6-11 details the forms of biliary disease and contrasts the lab findings associated with each.

History/PE

- **Postprandial abdominal pain** (usually in the **RUQ**) that radiates to the right subscapular area or the epigastrium, often associated with **nausea and vomiting,** dyspepsia, and flatulence.
- **Gallstones:** May have RUQ tenderness and a palpable gallbladder or be asymptomatic.

KEY FACT

Pigmented gallstones result from hemolysis (black) or infection (brown).

Diagnosis

RUQ ultrasound: Initial and **definitive test** (see Figure 2.6-15).

KEY FACT

Most gallstones are precipitations of cholesterol and are not radiopaque.

Treatment

Cholecystectomy is curative and recommended for patients with symptomatic gallstones. Asymptomatic gallstones do not require treatment.

TABLE 2.6-11. Disorders Caused by Gallstones

Disorder	Definition	Presentation	Labs	Diagnosis	Management
Cholelithiasis	Stones in the gallbladder.	May be asymptomatic, or may cause biliary colic; transient RUQ pain commonly seen after eating fatty meals; due to temporary occlusion of the cystic duct by a stone.	Normal total bilirubin/alkaline phosphatase, serum amylase.	Ultrasonography.	If asymptomatic, observation; if symptomatic, laparoscopic cholecystectomy.
Cholecystitis	Inflamm tion of the gallbladder, typically due to stone occluding the cystic duct.	RUQ pain, fever (maybe), Murphy sign (cessation of inspiration with palpation of RUQ).	↑ WBC, normal total bilirubin/alkaline phosphatase, amylase.	Ultrasonography, HIDA scan.	Laparoscopic cholecystectomy; if patient is too ill to undergo surgery, transcutaneous drainage of gallbladder.
Choledocholithiasis	Stone in CBD.	Jaundice, ± RUQ pain, afebrile.	Normal/↑ WBC, ↑ total bilirubin/ alkaline phosphatase, ↑ amylase/lipase (if pancreatitis is present).	Ultrasonography often does not show the stone but may show dilated CBD. MRCP and ERCP are definiti e.	ERCP to remove stone, followed by cholecystectomy.
Cholangitis	Infection of the CBD, usually due to stone in CBD.	Charcot triad: RUQ pain, fever, jaundice, Reynolds pentad: Charcot triad + shock and altered mental status.	↑ WBC, ↑ total bilirubin/alkaline phosphatase.	Clinical diagnosis confi med by biliary dilation on imaging; or ERCP (both diagnostic and therapeutic).	ERCP; surgery if patient toxic.

ACUTE CHOLECYSTITIS

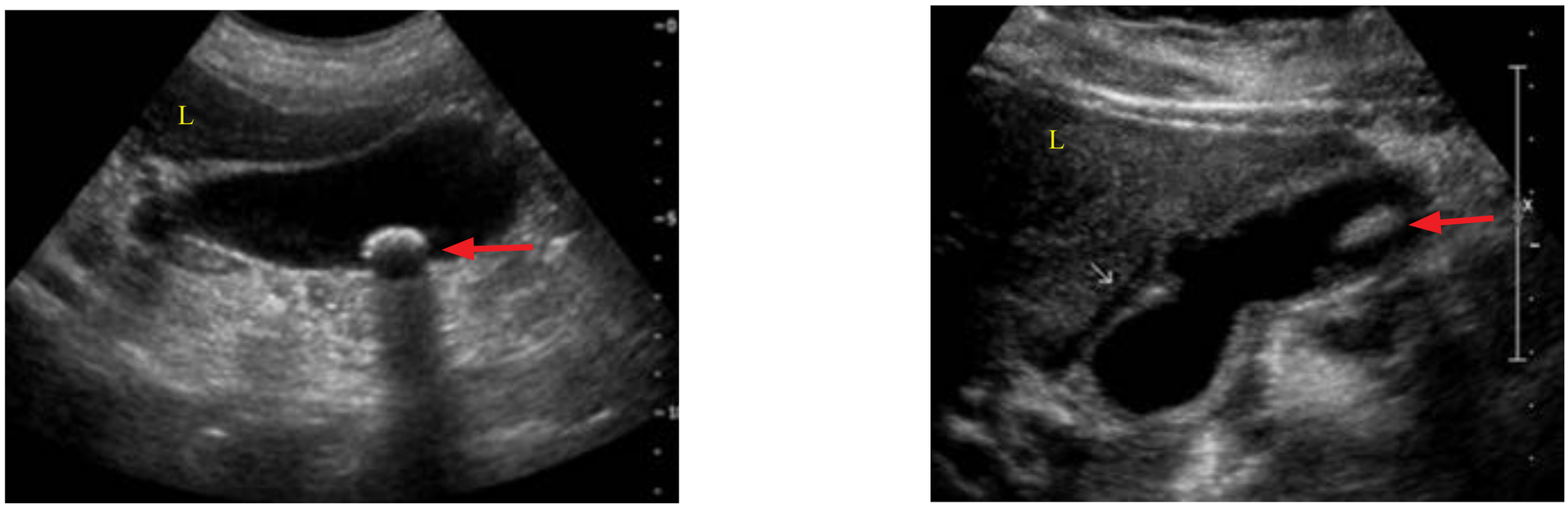
Prolonged blockage of the cystic duct by a gallstone that leads to progressive distention, inflammation, and infection. **Acalculous cholecystitis** occurs in the absence of cholelithiasis in patients who are chronically debilitated or critically ill.

History/Pe

- **History: RUQ pain, nausea, vomiting, and fever.**
- **Examination:** RUQ tenderness, inspiratory arrest with deep palpation of the RUQ **(Murphy sign),** and low-grade fever.

Q

A 35-year-old man with a 12-year history of ulcerative colitis presents to a clinic for annual follow-up. He has no current complaints. What is the most important screening test he should undergo?



A B

FIGURE 2.6-15. Gallstone disease. (A) Cholelithiasis. Ultrasound image of the gallbladder shows a gallstone (arrow) with posterior shadowing. **(B) Acute cholecystitis.** Ultrasound image shows a gallstone (red arrow), a thickened gallbladder wall (arrowheads), and pericholecystic fluid (white arrow). L = liver. (Reproduced with permission from USMLE-Rx.com.)

Diagnosis

- **Ultrasound (initial test):** May demonstrate stones, bile sludge, pericholecystic fluid, a thickened gallbladder wall, gas in the wall of the gallbladder, and/or an ultrasonic Murphy sign (see Figure 2.6-15).
- When ultrasound is equivocal, obtain a HIDA scan. In this nuclear medicine scan, which uses a radiotracer excreted through the biliary system, nonvisualization of the gallbladder suggests acute cholecystitis.

Treatment

- Give broad-spectrum **IV antibiotics** and **IV fluids.**
- **Cholecystectomy** is indicated.

CHOLEDOCHOLITHIASIS

- **Gallstones in the CBD.** Symptoms vary according to the degree of obstruction, the duration of the obstruction, and the presence/severity of infection.
- **Hx/PE:** Biliary colic, jaundice, afebrile unless current infection, and/or pancreatitis.
- **Dx: ↑ alkaline phosphatase** and **total and direct bilirubin** (see Table 2.6-11).
- **Tx:** Management consists of ERCP with sphincterotomy followed by cholecystectomy.

ACUTE CHOLANGITIS

- An acute bacterial infection of the biliary tree that commonly occurs 2° to **obstruction,** usually from **gallstones (choledocholithiasis).**
- **Other etiologies:** Bile duct stricture, primary sclerosing cholangitis, and malignancy. Gram-⊖ enterics are commonly identified pathogens.

History/Pe

- **Charcot triad—RUQ pain, jaundice,** and **fever/chills**—is classic.
- **Reynolds pentad**—Charcot triad plus septic **shock** and **altered mental status**—may be present in acute suppurative cholangitis.

KEY FACT

Charcot triad consists of RUQ pain, jaundice, and fever/chills. Reynolds pentad consists of RUQ pain, jaundice, fever/chills, shock, and altered mental status.

A

Colonoscopy. Patients with ulcerative colitis are at significantly ↑ risk of colon cancer. Thus, colonoscopies are recommended for such patients every 1–2 years beginning 8–10 years after diagnosis. If dysplasia is present on random biopsy, total colectomy is recommended.

Diagnosis

- **Labs: Leukocytosis, ↑ bilirubin,** and ↑ **alkaline phosphatase** (see Table 2.6-11); blood cultures.
- **Ultrasound (initial):** Diagnostic for CBD dilation.
- **ERCP (definitive):** Is both diagnostic and therapeutic.

Treatment

- Patients often require **ICU admission** for monitoring, hydration, BP support, and broad-spectrum **IV antibiotic treatment.**
- Patients with acute suppurative cholangitis require **emergent bile duct decompression** via ERCP/sphincterotomy, percutaneous transhepatic drainage, or open decompression.

GALLSTONE ILEUS

- Mechanical obstruction resulting from the passage of a large (> 2.5 cm) stone into the bowel through a cholecystoduodenal fistula. Obstruction is often at the ileocecal valve.
- **Hx/PE:** The classic presentation is a subacute SBO in an elderly woman. Patients may have no history of biliary colic.
- **Dx:** AXR with characteristics of SBO and pneumobilia (gas in the biliary tree) confirms the diagnosis. Upper GI barium contrast images will demonstrate no contrast in the colon.
- **Tx:** Laparotomy with stone extraction; closure of the fistula and cholecystectomy.

Liver Disease

ABNORMAL LIVER FUNCTION TESTS

Liver diseases can be divided into several patterns based on LFT results:

- **Hepatocellular injury:** ↑ AST and ALT.
- **Cholestasis: ↑ alkaline phosphatase and bilirubin.**
- **Mixed: Combination of hepatocellular and cholestatic picture.**
- **Isolated hyperbilirubinemia:** ↑ bilirubin.

Jaundice is a clinical sign that occurs when bilirubin levels exceed 2.5 mg/dL. Figures 2.6-16 and 2.6-17 summarize the clinical approaches toward cholestasis and isolated hyperbilirubinemia.

HEPATITIS

Inflammation of the liver leading to cell injury and necrosis. Hepatitis can be either acute or chronic.

- **Acute:** The most common causes are viruses (HAV, HBV, HCV, HDV, HEV) and drugs (alcohol, acetaminophen, INH, methyldopa).
  - **Fulminant:** Also known as acute liver failure. Severe liver injury with INR > 1.5 and hepatic encephalopathy in a patient without underlying chronic liver disease.
- **Chronic:** The most common causes are chronic viral infection (HCV most common in the United States, HBV worldwide), alcohol, autoimmune hepatitis, and metabolic syndromes (Wilson disease, hemochromatosis, α_1-antitrypsin deficiency).

KEY FACT

HCV is Chronic; 70–80% of patients with HCV infection will develop chronic hepatitis.

Q

A 43-year-old woman presents to the ED with nausea, vomiting, and epigastric pain. She has complained of intermittent RUQ pain for the past several months. Physical examination reveals marked epigastric tenderness. Labs show leukocytosis, ↑ AST and ALT, and ↑ lipase. AXR is unremarkable. What is the most likely diagnosis?

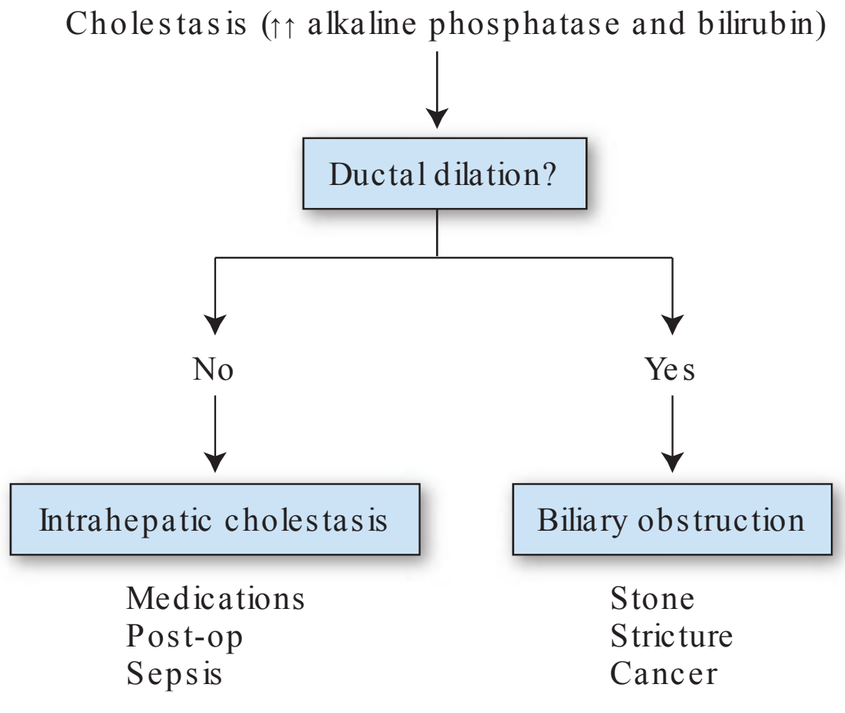


FIGURE 2.6-16. Approach to cholestasis.

KEY FACT

An **AST**/ALT ratio > 2 suggests alcohol hepatitis: you're to**AST**ed.

History/Pe

- **Acute hepatitis:**
  - Often begins with a nonspecific viral prodrome (**malaise,** fever, joint pain, fatigue, URI symptoms, **nausea, vomiting,** changes in bowel habits) followed by **jaundice** and RUQ tenderness. Examination often reveals jaundice, scleral icterus, and tender hepatomegaly.
  - HAV and HEV have only a self-limited acute phase; HBV and HCV may feature a mild acute phase or none at all. Acetaminophen toxicity can cause a life-threatening hepatitis. Table 2.6-12 outlines further distinctions among these.
- **Chronic hepatitis:** May be asymptomatic, but may cause fatigue and joint and muscle pains. Jaundice and complications of portal hypertension (hepatic encephalopathy, ascites, esophageal varices) typically occur only when the disease progresses to cirrhosis. At least 80% of those infected with HCV and 10% of those with HBV in adulthood will develop persistent infection with chronic active hepatitis.

Diagnosis

- **Acute hepatitis:** Labs reveal markedly ↑ **ALT and AST** and ↑ bilirubin/alkaline phosphatase.
- **Chronic hepatitis:** ALT and AST are either mildly elevated or even normal/low for > 3–6 months. Contrast this with the marked elevation of acute hepatitis as above.

A

Gallstone pancreatitis results from a gallstone that travels through the CBD and lodges at the ampulla of Vater, thus obstructing the flow of both pancreatic exocrine enzymes and bile. It most commonly occurs in women, who often report a history of biliary colic. Treatment involves management of the pancreatitis with supportive care and elective cholecystectomy.

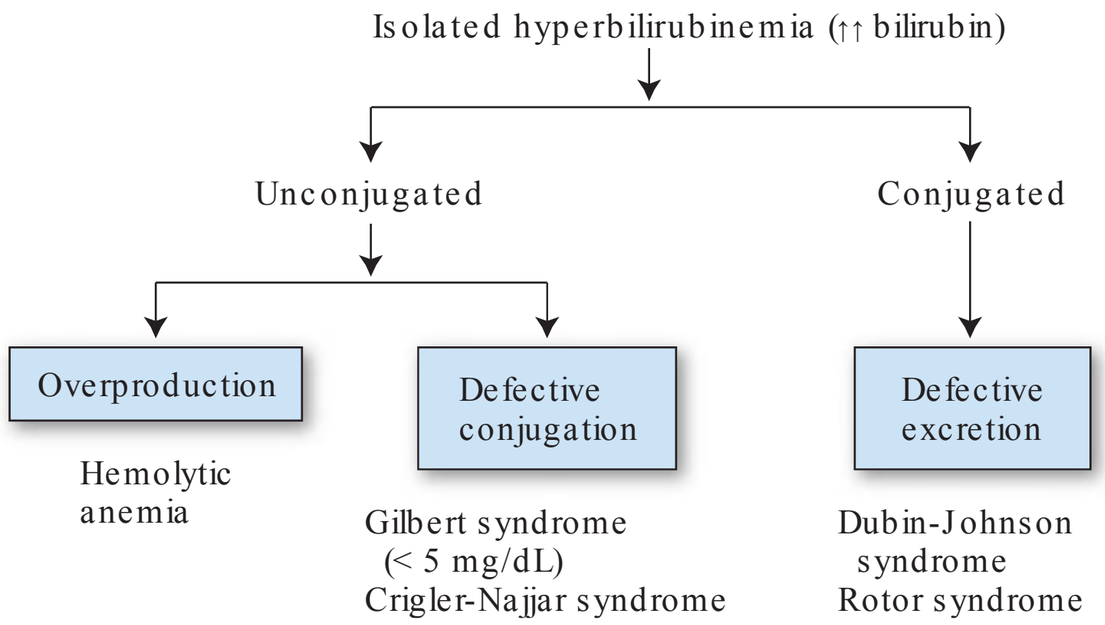


FIGURE 2.6-17. Approach to isolated hyperbilirubinemia.

TABLE 2.6-12. Types of Hepatitis

Virus type	Mode of transmission	Presentation	Notes
HAV	Fecal-oral	Typically self-limited acute hepatitis. May lead to fulminant hepatic failure.	Most common cause of acute viral hepatitis worldwide.
HBV	Bodily fluid	May be asymptomatic, but may present as viral prodrome (this is listed above) and/or jaundice. May lead to fulminant hepatic failure and require treatment with antivirals or liver transplant in severe cases.	< 10% of infections in adults become chronic, while most vertically transmitted become chronic. Extremely high transmission rate.
HCV	Bodily fluid	Asymptomatic or viral prodrome and/or jaundice.	80% become chronic. Less likely to be sexually transmitted than HBV; may present with very mild acute phase. Very rarely leads to acute liver failure.
HDV	Bodily fluid	Co-infection with HBV or superinfection in patient with prior HBV (more severe).	Requires HBV surface antigen. HDV is **D**ependent on HBV.
HEV	Fecal-oral	Typically self-limited acute hepatitis similar to HAV.	High mortality rate in pregnancy women. May become chronic in immunosuppressed patients.

- Diagnosis of viral hepatitis is made by **hepatitis serology** (see Table 2.6-13 and Figure 2.6-18 for a description and timing of serologic markers). May require liver biopsy if diagnosis is uncertain or to rule out other causes of liver disease in chronic or severe cases.
- Other diagnostic studies include the following:
  - **Autoimmune hepatitis:** ⊕ anti-nuclear and anti–smooth muscle antibodies (type 1) and anti-liver-kidney microsomal-1 antibodies and anti-

TABLE 2.6-13. Key Hepatitis Serologic Markers

Serologic Marker	Description
IgM HAVAb	IgM antibody to HAV; the best test to detect acute HAV.
HBsAg	Antigen found on the surface of HBV; continued presence indicates carrier state.
HBsAb	Antibody to HBsAg; **indicates immunity** to HBV.
HBcAg	Antigen associated with core of HBV. Not measured in clinical practice.
HBcAb	Antibody to HBcAg; IgM ⊕ during the **window period.** IgG HBcAb is an indicator of prior or current infection.
HBeAg	A different antigenic determinant in the HBV core. An important indicator of transmissibility (**BE**ware!).
HBeAb	Antibody to e antigen; indicates low transmissibility.

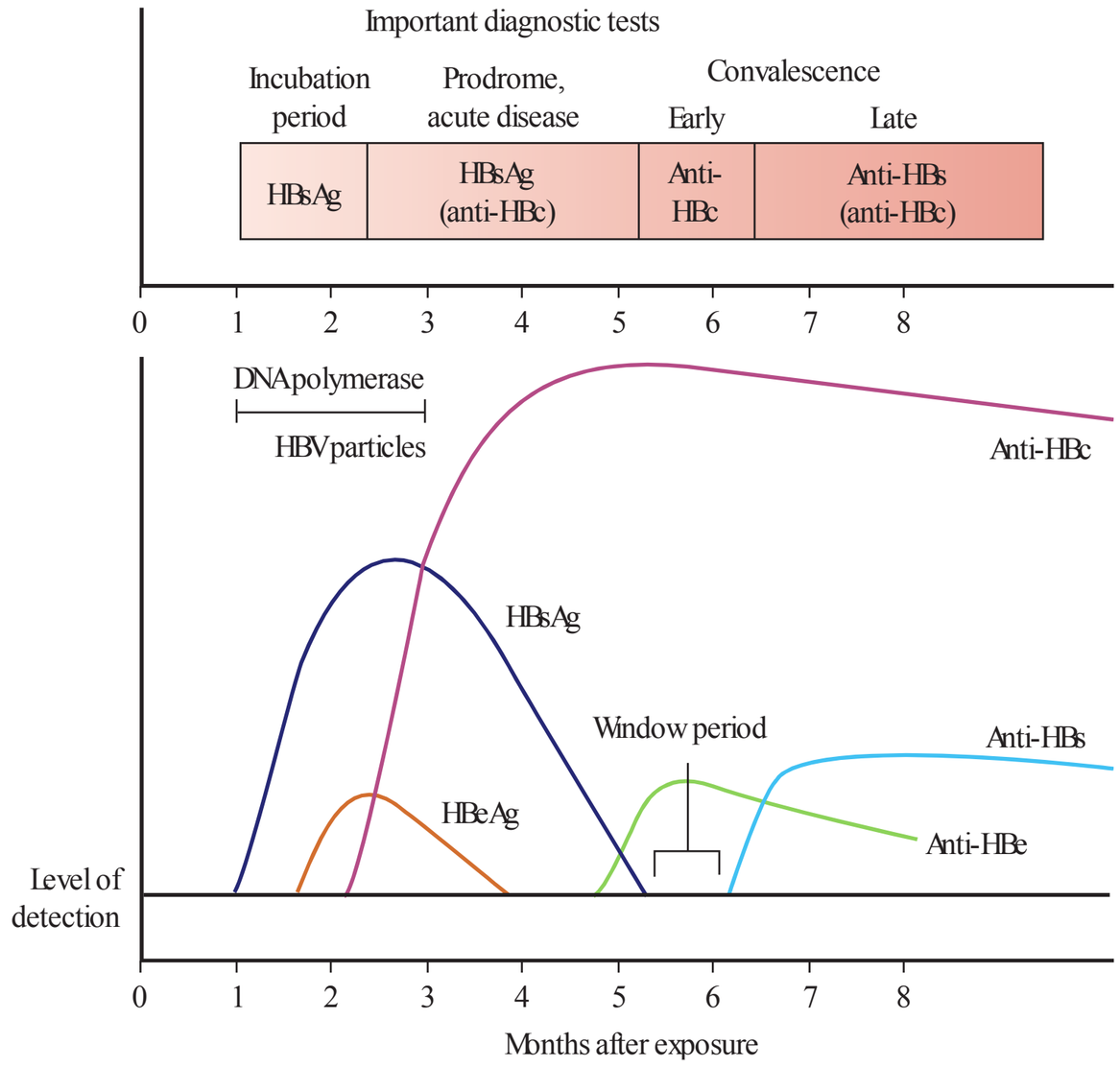


FIGURE 2.6-18. Time course of hepatitis B with serologic markers. (Reproduced with permission from Le T et al. First Aid for the USMLE Step 1 2015. New York, NY: McGraw-Hill; 2015.)

liver cytosol antibodies (type 2). May also present with elevated serum gamma globulins (IgG) and p-ANCA.

- **Hemochromatosis:** ↑ ferritin and transferrin saturation > 50%. Liver biopsy showing high hepatic iron index.
- **Wilson disease:** ↓ ceruloplasmin, ↑ urine copper, Kayser-Fleischer rings. Liver biopsy if diagnosis is uncertain.

Treatment

- **Acute hepatitis:** Generally supportive care. Acute HBV may require treatment with antivirals.
- **Chronic hepatitis:** Treatment is etiology specific.
  - **Chronic HBV infection:** Tenofovir and entecavir are most commonly used and have the least viral resistance. Other agents include telbivudine, adefovir, and lamivudine, but they are not recommended due to high rate of resistance.
  - **Chronic HCV infection: Medications and treatment duration vary based on genotype, cirrhosis status, and history of prior treatment. Typically either two direct-acting antivirals (DAAs) or one DAA plus ribavirin. Interferon is still used occasionally today.** This field is rapidly evolving. Previously, interferon and ribavirin, plus a protease inhibitor for some genotypes.
  - **Liver transplantation** is the definitive treatment for patients with end-stage liver failure. Emergent transplantation is indicated in cases of fulminant hepatic failure.

KEY FACT

The sequelae of chronic hepatitis include cirrhosis, portal hypertension, liver failure, and hepatocellular carcinoma.

Complications

Cirrhosis, liver failure, hepatocellular carcinoma (3–5%).

CIRRHOSIS

- **Bridging fibrosis and nodular regeneration** resulting from chronic hepatic injury.
- Most common etiologies in the United States are alcohol, chronic HCV, and non-alcoholic steatohepatitis. Etiologies can be intrahepatic or extrahepatic:
  - **Intrahepatic:** All causes of chronic hepatitis.
  - **Extrahepatic:**
    - Biliary tract disease (primary biliary cirrhosis, primary sclerosing cholangitis).
    - Posthepatic causes include right-sided heart failure, constrictive pericarditis, and Budd-Chiari syndrome (hepatic vein thrombosis 2° to hypercoagulability).

History/Pe

- **Hx: May be asymptomatic,** though may present with **jaundice, easy bruising (coagulopathy),** and **complications of portal hypertension such as ascites, hepatic encephalopathy** (asterixis, altered mental status), **gastroesophageal varices,** and thrombocytopenia. Ascites can be complicated by **spontaneous bacterial peritonitis.**
- **PE:** May reveal an enlarged, palpable, or firm liver and other signs of portal hypertension and liver failure (see Figures 2.6-19 and 2.6-20).

Diagnosis

- **Synthetic dysfunction (initial tests): ↓ albumin, ↑ PT/INR,** and **↑ bilirubin.**
- **Portal hypertension:** Thrombocytopenia (2° to hypersplenism, sequestration of platelets in the liver, and ↓ thrombopoietin production), varices, ascites (paracentesis).
- **Tissue (definitive):** Biopsy will show bridging fibrosis and nodular regeneration.
- **Etiology:** Hepatitis serologies, autoimmune markers, serum ferritin, ceruloplasmin, and α_1-antitrypsin.

KEY FACT

Spontaneous bacterial peritonitis is diagnosed by > 250 PMNs/mL in the ascitic fluid.

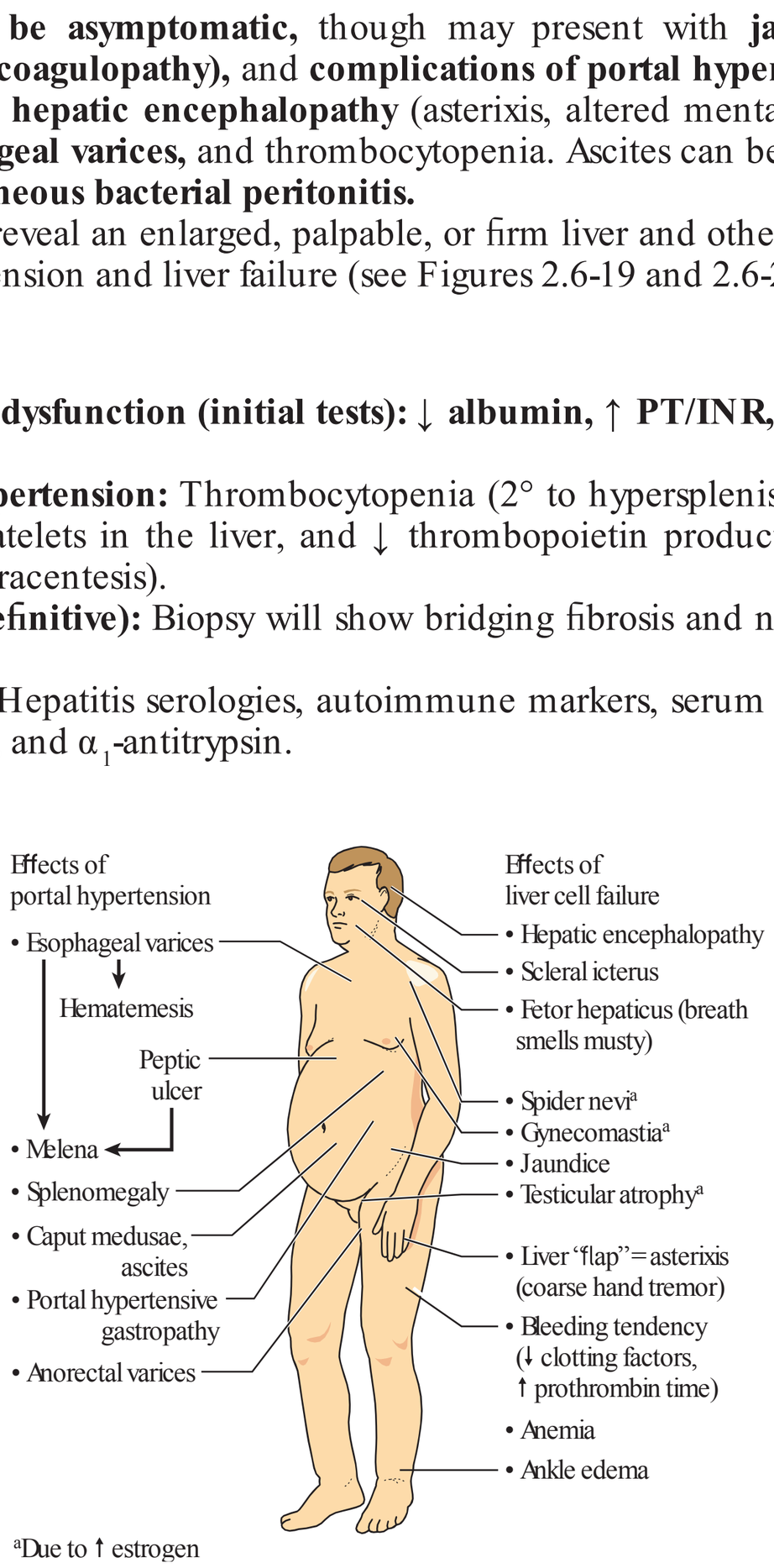


FIGURE 2.6-19. Presentation of cirrhosis/portal hypertension. (Reproduced with permission from Le T et al. First Aid for the USMLE Step 1 2015. New York, NY: McGraw-Hill; 2015.)

Q

A 21-year-old college student in the midst of final exams presents to a local clinic with "yellow eyes." His physical examination is unremarkable except for scleral icterus, and a CBC and blood smear show no abnormalities. A comprehensive metabolic profile reveals a normal AST and ALT but elevated unconjugated bilirubin. What is the most likely diagnosis?

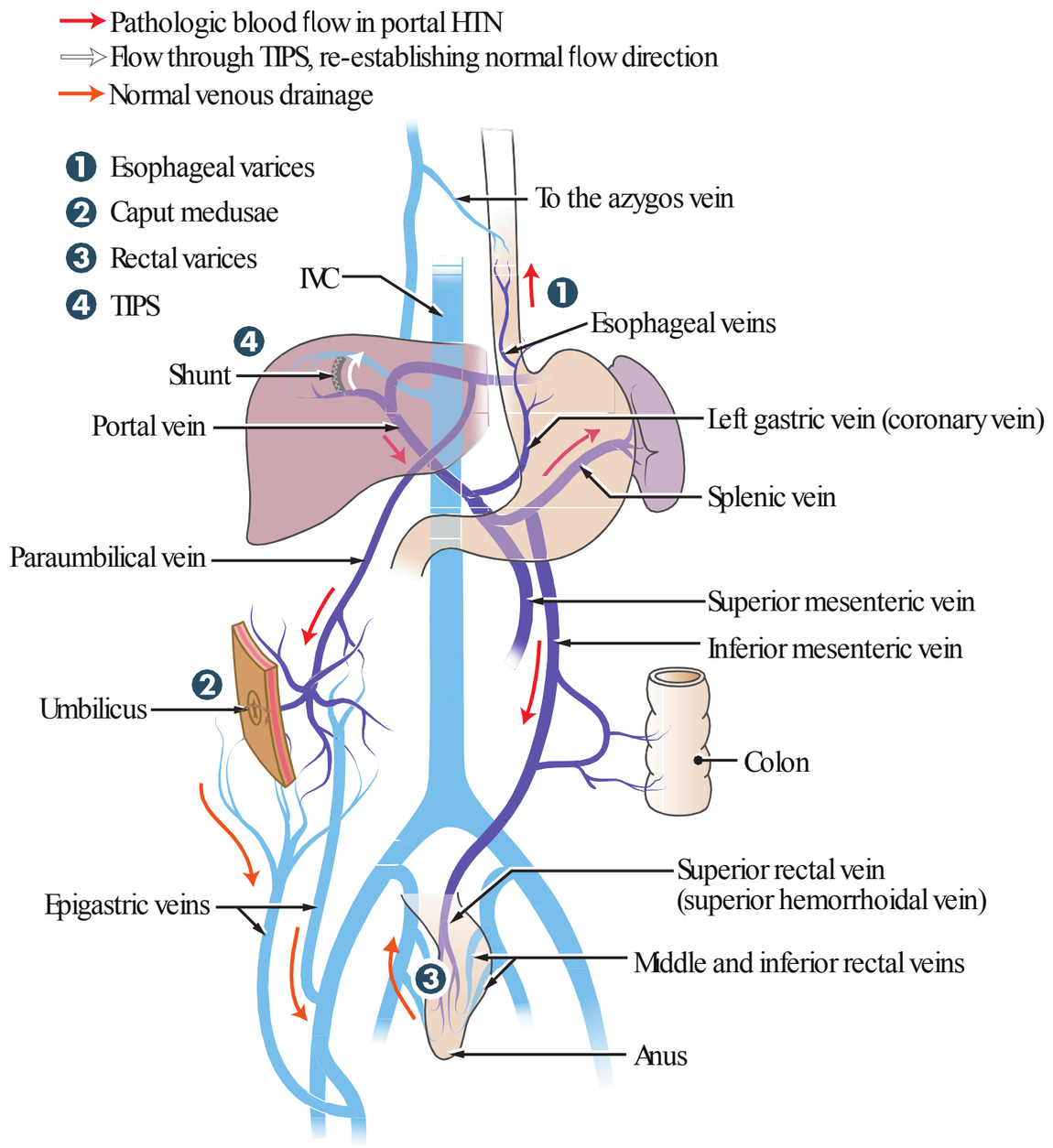


FIGURE 2.6-20. Portosystemic anastomoses. 1. Left gastric–azygous → esophageal varices. 2. Superior–middle/inferior rectal → hemorrhoids. 3. Periumbilical–inferior epigastric → caput medusae (navel). 4. Gastrorenal-splenorenal. 5. Retroperitoneal paravertebral. (Reproduced with permission from Le T et al. First Aid for the USMLE Step 1 2015. New York, NY: McGraw-Hill; 2015.)

- If ascites is present, the etiology of ascites can be determined by the **serum-ascites albumin gradient** (**SAAG** = serum albumin – ascites albumin); see Table 2.6-14.

Treatment

The goal is to treat and prevent the progression of cirrhosis and minimize factors that can lead to decompensation (see Table 2.6-15).

TABLE 2.6-14. Etiologies of Ascites by SAAG

SAAG > 1.1	SAAG < 1.1
Related to portal hypertension: ■ **Presinusoidal:** Splenic or portal vein thrombosis, schistosomiasis. ■ **Sinusoidal:** Cirrhosis. ■ **Postsinusoidal:** Right heart failure, constrictive pericarditis, Budd-Chiari syndrome.	Not related to portal hypertension: ■ Nephrotic syndrome. ■ TB. ■ Malignancy with peritoneal carcinomatosis (eg, ovarian cancer).

A

Gilbert syndrome is an autosomal recessive disorder of bilirubin glucuronidation due to ↓ activity of the enzyme glucuronyl transferase. Patients present with unconjugated hyperbilirubinemia but have a normal CBC, blood smear, and LFTs. The condition is benign, and no treatment is indicated.

TABLE 2.6-15. Complications of Cirrhosis

Complication	Mechanism/History	Management
Ascites	↑ portal hypertension results in transudative effusion. Physical examination reveals abdominal distention, fluid wave, and shifting dullness to percussion.	Sodium restriction and diuretics (furosemide, spironolactone); large-volume paracentesis. **TIPS** (**T**ransjugular **I**ntrahepatic **P**ortosystemic **S**hunt). Treat underlying liver disease if possible.
Spontaneous bacterial peritonitis	Presents with fever, abdominal pain, chills, nausea, and vomiting. Treatment indicated if diagnostic paracentesis reveals > 250 PMNs/mL.	IV antibiotics acutely (third-generation cephalosporin), IV albumin; prophylaxis with a fluoroquinolone to prevent recurrence. Development of SBP is associated with poor 1-year prognosis.
Hepatorenal syndrome	Acute prerenal failure in the setting of severe liver disease. Due to splanchnic vasodilation and decreased blood flow to the kidneys. A diagnosis of exclusion. Urinary sodium is < 10 mEq/L. "Healthy kidneys in an unhealthy environment."	Initially trial of volume repletion and rule out other causes of renal failure. May use octreotide (decrease splanchnic vasodilation) and midodrine (increase blood pressure). May require dialysis. Poor prognosis. Liver transplantation can be curative.
Hepatic encephalopathy	↓ clearance of ammonia; often precipitated by dehydration, infection, electrolyte abnormalities, and GI bleeding.	Lactulose, and/or rifaximin. Correct underlying triggers.
Esophageal varices	Portal hypertension leads to ↑ flow through portosystemic anastomoses.	Endoscopic surveillance in all patients with cirrhosis; medical prophylaxis with β-blockers or endoscopic band ligation to prevent bleeding in patients with known varices. For acute bleeding, endoscopy with band ligation or sclerotherapy is indicated. Urgent TIPS in refractory cases (associated with high mortality).
Coagulopathy	Impaired synthesis of all clotting factors (except VIII).	For acute bleeding, administer fresh frozen plasma. **Vitamin K will not correct coagulopathy.**

PRIMARY SCLEROSING CHOLANGITIS

- An idiopathic disorder characterized by progressive inflammation and fibrosis accompanied by strictures of extrahepatic and intrahepatic bile ducts. The disease usually presents in **young men with ulcerative colitis.** Patients are at ↑ **risk for cholangiocarcinoma.**
- **Hx/PE:** Presents with progressive **jaundice, pruritus,** and **fatigue.**
- **Dx:**
  - Laboratory findings include ↑ **alkaline phosphatase** and ↑ bilirubin.
  - MRCP/ERCP show **multiple bile duct strictures** and dilatations **("beading").**
  - Liver biopsy reveals periductal sclerosis ("onion skinning").
  - All newly diagnosed patients should undergo colonoscopy to evaluate for IBD.
- **Tx:** ERCP with dilation and stenting of strictures. Liver transplantation is the definitive treatment.

KEY FACT

Primary sclerosing cholangitis is strongly associated with ulcerative colitis.

KEY FACT

Primary biliary cirrhosis is an autoimmune disease that presents with jaundice and pruritus in middle-aged women.

PRIMARY BILIARY CIRRHOSIS

- **Autoimmune** disorder characterized by **destruction of intrahepatic bile ducts.** Most commonly presents in **middle-aged women** with other autoimmune conditions.
- **Hx/PE:** Presents with progressive **jaundice, pruritus,** and fat-soluble vitamin deficiencies (A, D, E, K).
- **Dx:** Laboratory findings include ↑ **alkaline phosphatase,** ↑ bilirubin, ⊕ **antimitochondrial antibody,** and ↑ cholesterol.
- **Tx:** Ursodeoxycholic acid (slows progression of disease); cholestyramine for pruritus; liver transplantation.

NON-ALCOHOLIC FATTY LIVER DISEASE

- Steatosis of hepatocytes leads to liver injury. Some patients progress to non-alcohol steatohepatitis (NASH) and are at risk of liver fibrosis and cirrhosis.
- Associated with insulin resistance and the metabolic syndrome.
- **Dx:** Largely a diagnosis of exclusion. Liver biopsy may show steatosis or steatohepatitis.
- **Tx:** Weight loss, diet, and exercise. If non-alcoholic steatohepatitis is present, consider vitamin E and pioglitazone.

HEPATOCELLULAR CARCINOMA

- One of the most common cancers worldwide despite its relatively low incidence in the United States.
- **Risk factors:** In the United States risk factors are **cirrhosis** (from alcohol, HCV, and non-alcoholic steatohepatitis) and **chronic hepatitis B (even without cirrhosis).** In developing countries, **HBV infection** and **aflatoxins** (in various food sources) are major risk factors.

History/PE

- Patients commonly present with **RUQ tenderness, abdominal distention,** and signs of chronic liver disease such as **jaundice, easy bruisability,** and **coagulopathy.** May present as decompensation of previously compensated cirrhosis.
- Examination may reveal tender **enlargement** of the liver.

Diagnosis

Often suggested by the presence of a mass on **ultrasound** or **CT** as well as by abnormal LFTs and significantly elevated α-fetoprotein (AFP) levels. Biopsy is required if diagnosis is uncertain.

Treatment

- **Surgical:** Partial hepatectomy if technically feasible and synthetic function preserved; orthotopic liver transplantation in patients with cirrhosis is preferred treatment if there are only a few small tumors (Milan criteria: single lesion < 5 cm or 3 lesions < 3 cm).
- **Nonsurgical:** Transarterial chemoembolization (TACE) and/or radiofrequency ablation. Sorafenib for advanced metastatic disease.
- May monitor AFP levels (if previously elevated) and serial surveillance imaging (US, CT) to screen for recurrence.

HEMOCHROMATOSIS

A state of iron overload in which hemosiderin accumulates in the liver, pancreas (islet cells), heart, adrenals, testes, and pituitary.

- **1° hemochromatosis:** An autosomal recessive disease characterized by mutations in the HFE gene that result in excessive absorption of dietary iron.
- **2° hemochromatosis:** Occurs in patients receiving chronic transfusion therapy (eg, sickle cell disease or α-thalassemia).

History/Pe

- **Hx:** Patients may present with abdominal pain, **DM, hypogonadism, arthropathy of the MCP joints, heart failure,** impotence, or cirrhosis.
- **Examination: Bronze skin pigmentation, cardiac dysfunction** (CHF), hepatomegaly, and testicular atrophy. Labs may reveal evidence of DM.
- Hemochromatosis does not affect the lung, kidney, or eye.

Diagnosis

- ↑ **serum iron,** percent saturation of iron, and ferritin with ↓ serum transferrin.
- A transferrin saturation (serum iron divided by TIBC) > 45% is highly suggestive of iron overload.
- Perform a **liver biopsy** (to determine hepatic iron index), MRI, or HFE gene mutation screen.

Treatment

- **Weekly phlebotomy** to normalize serum iron levels, and then maintenance phlebotomy every 2–4 months.
- Iron chelating agents such as **deferoxamine,** deferiprone, or deferasirox can be used for maintenance therapy.

Complications

Cirrhosis, hepatocellular carcinoma, restrictive cardiomyopathy, arrhythmias, DM, impotence, arthropathy, hypopituitarism.

WILSON DISEASE (HEPATOLENTICULAR DEGENERATION)

- An autosomal recessive disorder that results in defective copper transport and subsequent accumulation and deposition of copper in the liver and brain. Usually occurs in patients < 30 years of age; 50% are symptomatic by age 15.
- **Hx:** Patients present with hepatitis/cirrhosis, neurologic dysfunction (ataxia, **tremor**), and **psychiatric abnormalities** (psychosis, anxiety, mania, depression).
- **PE:** May reveal **Kayser-Fleischer rings** (green-to-brown deposits of copper in Descemet membrane; see Figure 2.6-21) as well as jaundice, hepatomegaly, asterixis, choreiform movements, and rigidity.
- **Dx: ↓ serum ceruloplasmin,** ↑ 24-hour urinary copper excretion. Liver biopsy if diagnosis is uncertain.
- **Tx: Penicillamine** or **trientine** (copper chelators that ↑ urinary copper excretion), **dietary copper restriction** (avoid shellfish, liver, legumes), and zinc (↑ fecal excretion).

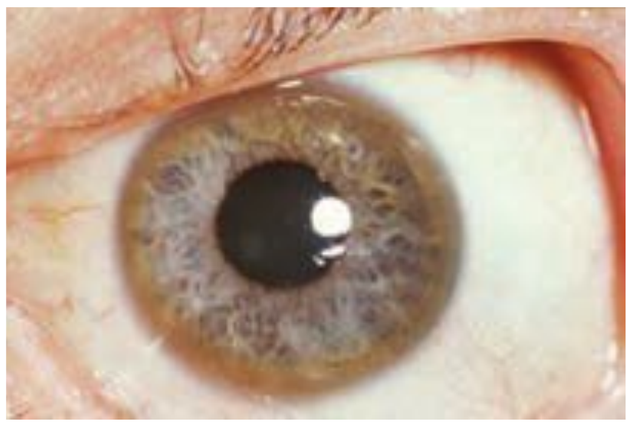


FIGURE 2.6-21. Kayser-Fleischer ring. Note the brown ring encircling the iris. This is a result of copper deposition in Descemet membrane and is a classic finding in Wilson disease. (Reproduced with permission from USMLE-Rx.com.)

Q

A 36-year-old woman with a past medical history of hypercholesterolemia and type 2 DM presents with intermittent dull RUQ discomfort. The patient does not drink alcohol. Her physical examination is unremarkable. Lab studies show elevated AST and ALT but are otherwise normal. Hepatitis serologies are ⊖. What is the most likely diagnosis?

Pancreatic Disease

INSULINOMA

- Results from insulin-producing tumor, associated with MEN type 1, usually benign.
- **Hx:** Hypoglycemia satisfying Whipple triad: (1) documented hypoglycemia on a venipuncture; (2) with associated symptoms including sweating, palpitations, anxiety, tremors, headache, confusion; and (3) resolution of symptoms with correction of hypoglycemia.
- **Dx:**
  - **Lab tests (initial tests):** Fasting serum insulin (elevated), C-peptide (elevated).
  - **72-hour fasting (definitive test):** Patient develops profound or symptomatic hypoglycemia after prolonged fast. Once hypoglycemia is reached, labs drawn to determine etiology: glucose, serum insulin level (elevated), C-peptide level (elevated), sulfonylurea screen (negative), serum beta hydroxybutyrate level (low), serum cortisol level (normal/elevated).
  - **Tumor localization:** transabdominal ultrasound, CT, MRI, endoscopic ultrasound, or selective arterial calcium stimulation.
- **Tx:** Surgery to resect tumor.

VIPOMA

- Results from VIP-producing tumor, highly malignant.
- **Hx:** Watery diarrhea, dehydration, muscle weakness, flushing.
- **Dx:**
  - **Stool sample:** Low stool osmotic gap (ie, secretory diarrhea).
  - **Lab tests:** High VIP levels, achlorhydria (because gastrin secretion is inhibited by VIP), hyperglycemia, hypercalcemia, hypokalemia.
  - **CT scan:** Localize the tumor.
- **Tx:** Initially, replace fluid and electrolyte losses. Surgery to resect tumor. May also consider octreotide.

KEY FACT

The hallmark finding in pancreatic cancer is a nontender, palpable gallbladder with jaundice.

PANCREATITIS

Table 2.6-16 outlines the features of acute and chronic pancreatitis.

PANCREATIC CANCER

- Most (75%) are adenocarcinomas in the head of the pancreas.
- **Risk factors:** Smoking, chronic pancreatitis, and a first-degree relative with pancreatic cancer. Incidence ↑ after age 45; slightly more common in men.

HISTORY/PE

- Presents with **abdominal pain** radiating toward the back as well as with **obstructive jaundice,** loss of appetite, nausea, vomiting, **weight loss,** weakness, fatigue, and indigestion. Often asymptomatic, and thus presents late in the disease course. In some patients, depression may be the most prominent symptom.
- Examination may reveal a palpable, nontender gallbladder **(Courvoisier sign)** or migratory thrombophlebitis **(Trousseau sign).**

A

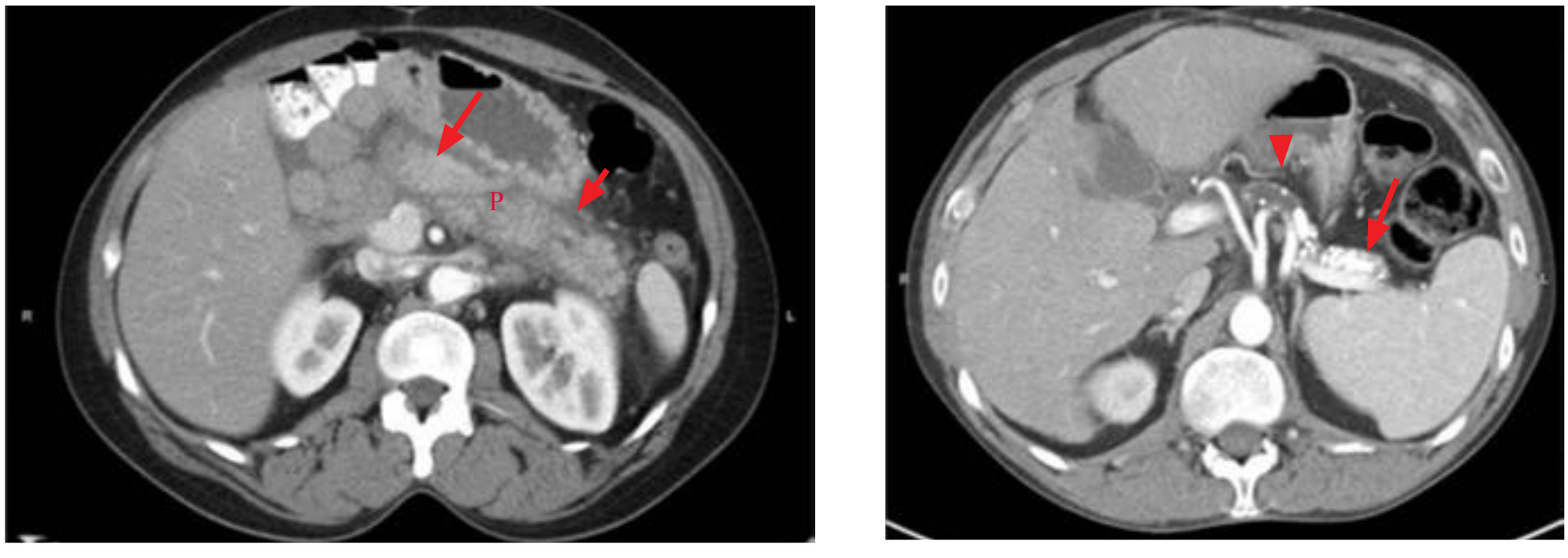
Non-alcoholic fatty liver disease (NAFLD), a condition that is associated with insulin resistance and metabolic syndrome.

TABLE 2.6-16. Features of Acute and Chronic Pancreatitis

Variable	Acute pancreatitis	Chronic pancreatitis
Pathophysiology	Leakage of activated pancreatic enzymes into pancreatic and peripancreatic tissue.	Irreversible parenchymal destruction leading to pancreatic dysfunction and insufficiency.
Time course	Abrupt onset of severe pain.	Persistent, recurrent episodes of severe pain.
Risk factors	**Gallstones, alcohol abuse,** hypercalcemia, hypertriglyceridemia, trauma (most common cause of acute pancreatitis in children), drug side effects (thiazide diuretics), viral infections, post-ERCP, scorpion bites.	**Alcohol abuse** (90%), gallstones, CF, smoking, pancreatic divisum, family history.
Hx/PE	**Severe epigastric pain (radiating to the back);** nausea, vomiting, weakness, fever, shock, pleural effusion, ARDS. Flank bruising **(Grey Turner sign)** and periumbilical discoloration **(Cullen sign)** may be evident on examination.	Recurrent episodes of **persistent epigastric pain;** anorexia, nausea, constipation, flatulence, **steatorrhea,** weight loss, DM.
Diagnosis	↑ **lipase (more sensitive and specific than amylase),** ↑ **amylase,** ↓ **calcium** if severe; **"sentinel loop"** or **"colon cutoff sign"** on AXR. Abdominal ultrasound or CT may show an enlarged pancreas with stranding, abscess, hemorrhage, necrosis, or pseudocyst (see Figure 2.6-22A).	↑ to normal amylase and lipase, ↓ stool elastase, **pancreatic calcifications** (see Figure 2.6-22B), and alternating stenosis and dilation of the main pancreatic duct on CT or US **("chain of lakes").**
Treatment	Removal of the offending agent if possible. Supportive care, including IV fluids/electrolyte replacement, analgesia, bowel rest, NG suction, nutritional support, and O_2. Infected pancreatic necrosis should be treated with antibiotics, though prophylactic antibiotics are not recommended. Endoscopic, percutaneous, or surgical debridement may be considered.	Analgesia, pancreatic enzyme replacement, avoidance of causative agents (EtOH), celiac nerve block; endoscopic dilation of pancreatic duct; surgery for intractable pain or structural causes.
Prognosis	Roughly 85–90% are mild and self-limited; 10–15% are severe, requiring ICU admission. Mortality may approach 50% in severe cases.	Patients can have chronic pain and pancreatic dysfunction.
Complications	**Pancreatic pseudocyst, fistula formation,** hypocalcemia, renal failure, pleural effusion, chronic pancreatitis, sepsis, and ARDS. Mortality 2° to acute pancreatitis can be predicted with Ranson criteria.	**Chronic pain,** opiate addiction, diabetes mellitus, malnutrition/weight loss, pancreatic cancer.

Diagnosis

- **CT scan with contrast (initial test):** Localize the tumor, and assess the extent of local invasion and distant metastases.
- If a mass is not visualized on CT, use endoscopic ultrasound ± ERCP.
- CA-19-9 is often elevated but is neither sensitive nor specific.



A B

FIGURE 2.6-22. Pancreatitis. (A) Uncomplicated acute pancreatitis. Peripancreatic fluid and fat stranding can be seen (arrows). P = pancreas. **(B) Chronic pancreatitis.** Note the dilated pancreatic duct (arrowhead) and pancreatic calcifications (arrow). (Reproduced with permission from USMLE-Rx.com.)

Treatment

- **Locally advanced or metastatic disease:** Most frequent presentation. Palliative chemotherapy or best supportive care.
- **Small tumors in the pancreatic head with no metastasis or major vessel involvement:** Whipple procedure (pancreaticoduodenectomy).
- Chemotherapy with 5-FU and gemcitabine may improve short-term survival, but long-term prognosis is poor (5–10% 5-year survival).
- **ERCP with stenting** to relieve patients presenting with obstructive symptoms.

HIGH-YIELD FACTS IN

HEMATOLOGY/ONCOLOGY

Coagulation Disorders 168
- Normal Hemostasis 168
- Hemophilia 168
- von Willebrand disease 169
- Hypercoagulable States 170
- Disseminated Intravascular coagulation 172
- Thrombotic Thrombocytopenic Purpura 172
- Idiopathic Thrombocytopenic Purpura 173

Red Blood Cell Disorders 173
- Anemias 173
- Thalassemias 180
- Polycythemias 180
- Blood Transfusion Reactions 182
- Porphyria 182

White Blood Cell Disorders 183
- Leukemias 183
- Lymphomas 186

Plasma Cell Disorders 189
- Multiple Myeloma 189
- Waldenström Macroglobulinemia 190
- Amyloidosis 190

Neutropenia 191

Eosinophilia 192

Transplant Medicine 193

Diseases Associated With Neoplasms 194

Coagulation Disorders

NORMAL HEMOSTASIS

Vascular injury leads to the release of von Willebrand factor (vWF) and tissue factor from subendothelial vessel walls. vWF facilitates attachment and aggregation of platelets, forming a platelet plug. Tissue factor triggers the coagulation cascade via the intrinsic pathway with factor VII, amplified by the intrinsic pathway. Ultimately the platelet plug and coagulation cascade create a **fibrin mesh,** as shown in Figure 2.7-1. Drugs affecting the cascade are shown in Table 2.7-1.

Heparin-to-warfarin bridge is necessary because proteins C and S have shorter half-lives than the other vitamin K–dependent factors (II, VII, IX, and X), leading to a transient period of **paradoxic hypercoagulability** before proper anticoagulation.

KEY FACT

Enteric bacteria synthesize vitamin K. Neonates lack these bacteria and are prone to bleeding unless given a vitamin K shot at birth.

HEMOPHILIA

X-linked clotting factor deficiencies of factors **VIII** (hemophilia **A, 80% of cases**), **IX** (hemophilia **B**), and **XI** (hemophilia **C**) that result in an ↑ **tendency to bleed.** Rarely, hemophilias can be **acquired** if antibodies against these factors are produced via autoimmune, lymphoproliferative, or postpartum states.

KEY FACT

Hemophilia **C** is most common in **Ashkenazi Jews** and is often **autosomal.**

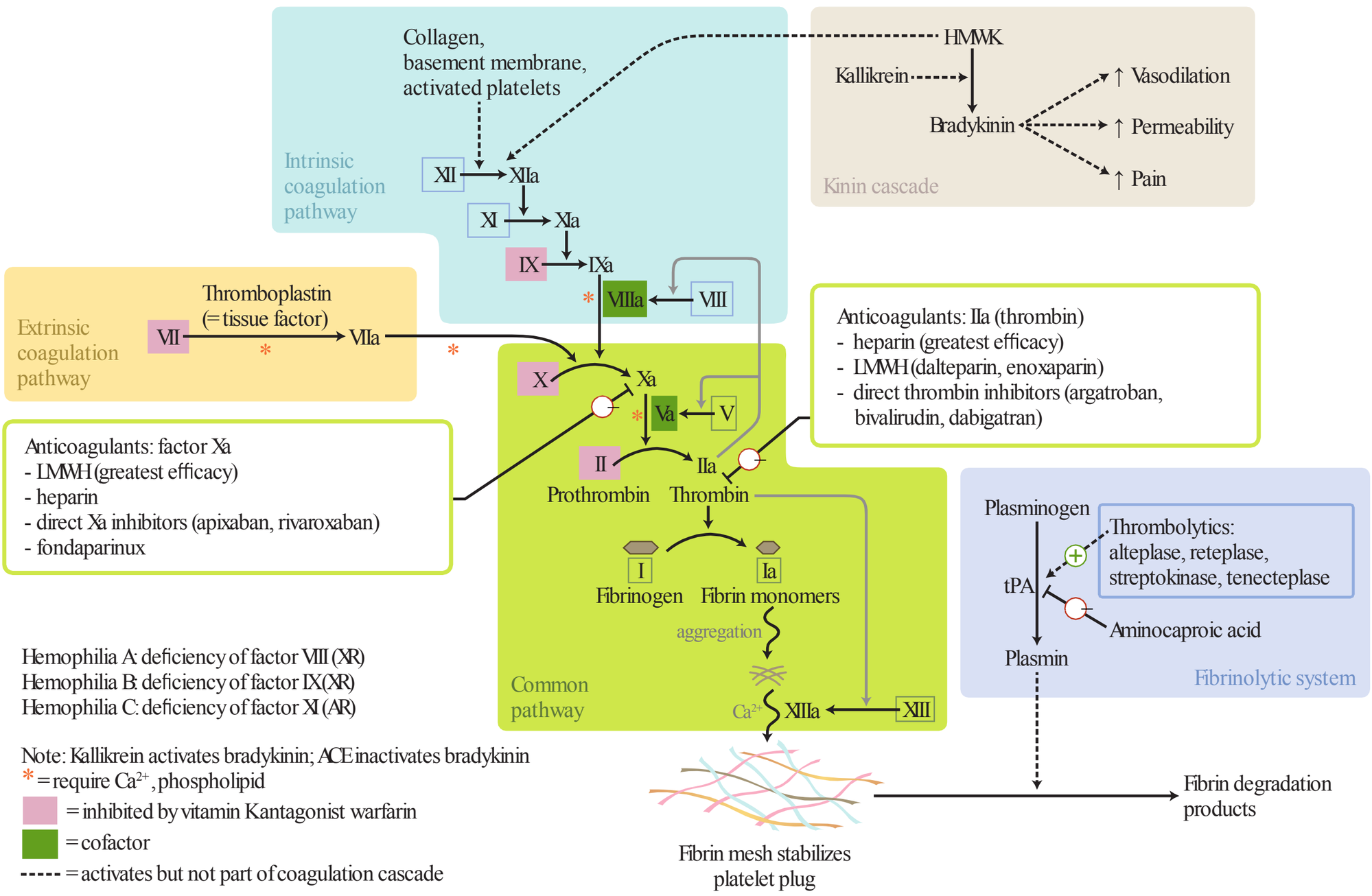


FIGURE 2.7-1. Coagulation cascade. (Adapted with permission from USMLE-Rx.com.)

TABLE 2.7-1. Coagulation Pharmacology

Medication	Mechanism	Lab Values	Misc
Heparin	Activates antithrombin.	↑ **PTT.**	Antidote is **protamine sulfate.** LMWH has more effect on factor Xa, can be given subcutaneously, and **does not increase PTT.**
Warfarin	Inhibits synthesis of vitamin K–dependent coagulation factors (II, VII, IX, X, proteins C and S).	↑ **PT.**	For rapid reversal give **FFP,** otherwise give **vitamin K.** Teratogen.
tPA	Aid conversion of plasminogen to plasmin, which breaks down fibrin.	↑ **PT,** ↑ **PTT.**	Treat toxicity with aminocaproic acid.
Factor **Xa** inhibitors (Api**XA**ban, Rivero**XA**ban)	Directly inhibit factor Xa.	**PT/PTT not monitored.**	**No reversal agent.**
LMWH (enoxaparin)	Mainly inhibits factor Xa.	**Anti-factor Xa,** although typically unmonitored.	Protamine less effective at reversal than for heparin.
Direct thrombin inhibitors (dabigatran, argatroban)	Directly inhibits factor II (thrombin).		No reversal agent.

History/Pe

- Presents as a young boy with **spontaneous hemorrhage** into the tissues and joints that, if untreated, can lead to **arthropathy and joint destruction.** Spontaneous **intracerebral,** renal, retroperitoneal, and GI hemorrhages are also seen.
- Mild cases may have major hemorrhage after surgery, trauma, or dental procedures but are otherwise asymptomatic.

Diagnosis

- ↑ PTT is prolonged on basic bleeding workup. PT and bleeding time are normal.
- Best initial test: **Mixing study.** Mix the patient's plasma with normal plasma, which will **correct the PTT** in hemophilia patients as it contains all clotting factors.
- Most accurate test: **Obtain specific factor assays** for factors VII, VIII, IX, XI, and XII.

Treatment

- If bleeding is severe or factor level is ≤ 1% of normal (severe), immediately transfuse missing factor or, if unavailable, cryoprecipitate.
- If bleeding is not severe and factor level is > 5% of normal (mild) or 1–3% of normal (moderate), hemophilia may be treated with **desmopressin (DDAVP),** which releases **factor VIII from endothelial cells.**

VON WILLEBRAND DISEASE

An **autosomal dominant** defect or deficiency in vWF with decreased levels of factor VIII, which is carried by vWF (see Figure 2.7-2). Symptoms are

KEY FACT

Cryoprecipitate consists mainly of factor VIII and fibrinogen, with smaller concentrations of factor XIII, vWF, and fibronectin. It is a more concentrated source of factor VIII and fibrinogen than FFP.

Q

An 8-year-old boy from eastern Europe presents with severe swelling and warmth of his knee several hours after a minor "bump" against a lamppost. What is the most accurate diagnostic test for his presentation?

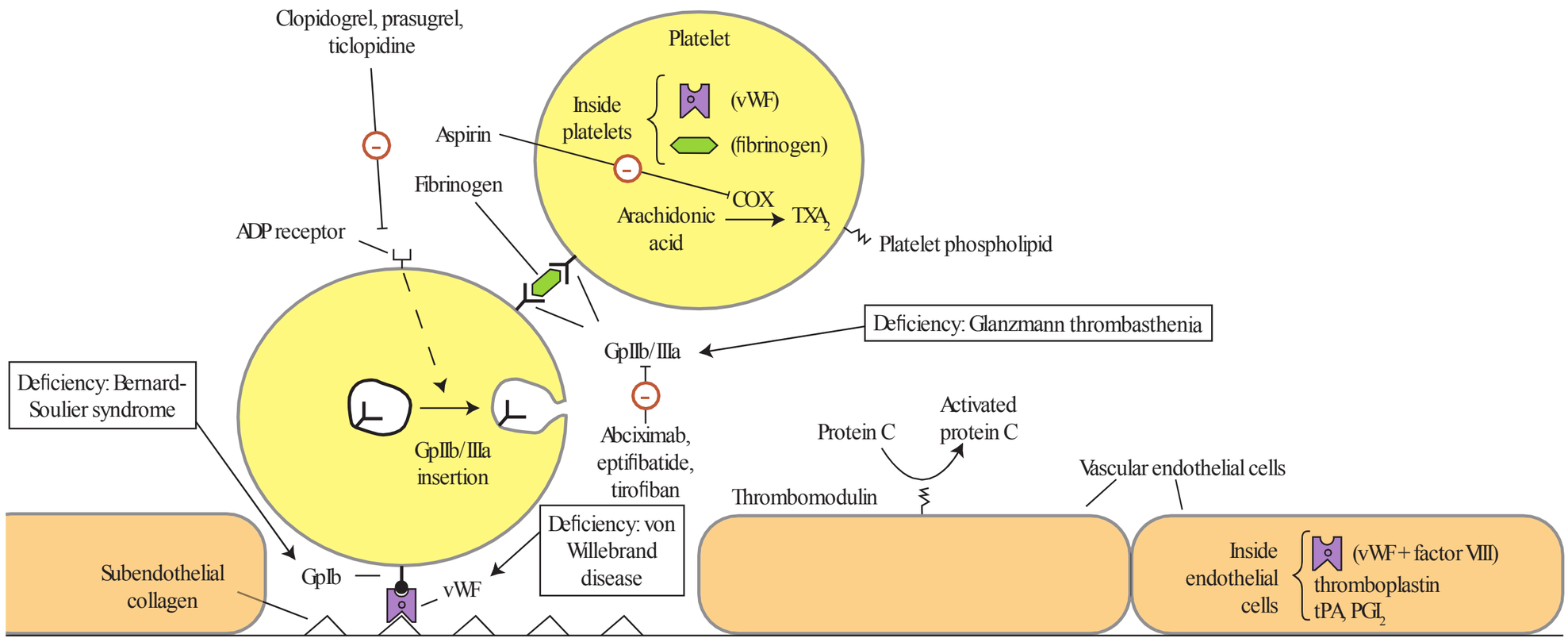


FIGURE 2.7-2. Thrombogenesis deficiencies. (Adapted with permission from Le T et al. First Aid for the USMLE Step 1 2015. New York, NY: McGraw-Hill; 2015.)

due to platelet dysfunction and deficient factor VIII, and are milder than in hemophilia. vWD is the **most common inherited bleeding disorder** (1% of the population), and the most common form of vWD is type 1 vWD (mild to moderate deficiency in vWD). Type 2 includes qualitative defects in vWD, and type 3 is absence of functional vWF.

History/Pe

- Often presents in childhood with **recurrent and prolonged** mucosal bleeding (epistaxis, gums, teeth, menorrhagia) and bleeding after dental or surgical procedures.
- Often a family history is present, and symptoms worsen with ASA use.

KEY FACT

Decreased agglutination seen on the ristocetin cofactor assay is diagnostic of vWD.

Diagnosis

- Initial bleeding workup will show an ↑ **bleeding time** in all vWD types. ↑ PTT as in hemophilia may be seen due to low factor VIII levels. **PT and platelet count will be normal.**
- Most accurate test: **Ristocetin cofactor assay** of patient plasma (measures capacity of vWF to agglutinate platelets) and **vWF antigen level.**

KEY FACT

ASA ↑ the risk of bleeding in patients with vWD.

Treatment

- Bleeding episodes in mild/moderate type 1 disease can be treated with **DDAVP.**
- Menorrhagia can be controlled with **OCPs.** Avoid ASA and platelet function inhibitors.

A

This boy (X-linked) probably has hemophilia A (most common), which is most accurately diagnosed with a specific factor VIII level.

HYPERCOAGULABLE STATES

Hypercoagulable states (thrombophilias or prothrombotic states) is an all-inclusive term describing conditions that ↑ **a patient's risk of developing thromboembolic disease.** Causes can be **genetic, acquired, or physiologic** (see Table 2.7-2). Three commonly tested causes are highlighted here, but all present similarly:

TABLE 2.7-2. Causes of Hypercoagulable States

Genetic	Acquired	Physiologic
Antithrombin III deficiency	Surgery	Pregnancy
Protein C deficiency	Trauma	Age
Protein S deficiency	Malignancy	
Factor V Leiden	Immobilization	
Hyperhomocysteinemia	Smoking	
Dysfibrinogenemia	Obesity	
Plasminogen deficiency	Antiphospholipid syndrome	
Prothrombin G20210A mutation	Nephrotic syndrome	
MTHFR gene mutation	OCPs/HRT	

- **Factor V Leiden:** A polymorphism in factor V, rendering it resistant to inactivation by activated protein C, is the most common cause of hereditary thromboembolic disease.
- **Heparin-induced thrombocytopenia (HIT):** An immunologic reaction to the administration of heparin creates platelet-activating antibodies, which leads to the formation of blood clots and a **rapid (50%) drop in platelet count.**
- **Antiphospholipid syndrome (APS):** Often associated with **SLE** and **rheumatoid arthritis,** APS predisposes to both arterial and venous thrombi formation and spontaneous abortions.

History/Pe

- Can present with **recurrent** thrombotic complications: **DVT, pulmonary embolism, arterial thrombosis, MI, and stroke.** Women may have recurrent miscarriages.
- HIT: Hospitalized patient on anticoagulation with a drop in platelets.
- Factor V Leiden: Young Caucasian patient with a personal and family history of thrombosis.
- APS: Middle-aged women with recurrent miscarriages or thrombosis.

Diagnosis

- Before a hereditary workup is conducted, acquired causes should be ruled out. Hereditary abnormality is **confirmed with two abnormal values obtained while the patient is asymptomatic and untreated, with similar values obtained in two other family members.**
- Specific tests to confirm HIT (PF4 antibody and serotonin release assay), APS (lupus anticoagulant and anticardiolipin antibody).

Treatment

- Patients with a hypercoagulable state **with DVT or pulmonary embolism** should be treated with heparin followed by 3–6 months of warfarin anticoagulation for the first event, 6–12 months for the second, and lifelong anticoagulation for subsequent events.
- If anticoagulation is contraindicated (recent trauma, hemorrhage, severe hypertension), an inferior vena cava filter is the next best step and is also considered for patients who have recurrent DVTs on anticoagulation.
- For HIT, first **discontinue heparin,** then start argatroban or lepirudin.
- Avoid OCPs in patients with factor V Leiden.

KEY FACT

Protein C or S deficiency: hypercoagulable state with **skin or tissue necrosis following warfarin administration.**

KEY FACT

Suspect PE in a patient with rapid onset of dyspnea, pleuritic chest pain, hypoxia, tachycardia, and an ↑ alveolar-arterial oxygen gradient without another obvious explanation.

Q

A 33-year-old woman was admitted to the hospital for anticoagulation after a pulmonary embolism. On day 4 of her stay, her platelet level ↓ from 150,000 to 60,000/mm^3 and her INR remains < 2. What is the next best step, and what complications can result from this condition?

DISSEMINATED INTRAVASCULAR COAGULATION

An acquired coagulopathy caused by **deposition of fibrin in small blood vessels,** leading to thrombosis and end-organ damage. **Depletion of clotting factors and platelets** leads to a bleeding diathesis. It is associated with many severe illnesses and is often seen in hospitalized patients.

History/PE

- Common associations with DIC: **Obstetric** complications, **sepsis,** neoplasms, acute promyelocytic leukemia, **pancreatitis,** hemolysis, vascular disorders (aortic aneurysm), massive trauma, drug reactions, acidosis, and ARDS.
- Clinical presentation:
  - **Acute:** Bleeding from venipuncture sites, into organs, with ecchymoses and petechiae.
  - **Chronic:** Bruising and mucosal bleeding, thrombophlebitis, renal dysfunction, and transient neurologic syndromes.

Diagnosis

- Diagnosed by clinical features and lab findings.
- DIC may be confused with liver disease, but **unlike liver disease, factor VIII is depressed.**

Treatment

Reverse the underlying cause; transfuse RBCs, platelets, FFP, and manage shock.

KEY FACT

DIC is characterized by both thrombosis and hemorrhage.

THROMBOTIC THROMBOCYTOPENIC PURPURA

A deficiency of the vWF-cleaving enzyme **(ADAMTS-13)** resulting in abnormally large vWF multimers that aggregate platelets and create **platelet microthrombi.** These block off small blood vessels, leading to end-organ damage. **RBCs are fragmented** by contact with the microthrombi, leading to hemolysis (microangiopathic hemolytic anemia). The ADAMTS-13 deficiency is either inherited or often acquired secondary to infection.

KEY FACT

The three causes of microangiopathic hemolytic anemia are HUS, TTP, and DIC.

History/PE

Maintain high clinical suspicion for TTP if three of these five symptoms are present:

- Low platelet count
- Microangiopathic hemolytic anemia
- Neurologic changes (delirium, seizure, stroke)
- Impaired renal function
- Fever

MNEMONIC

Remember—

DICk's **H**o**US**e got **TTP**ed because he caused microangiopathic hemolytic anemia.

Diagnosis

- Clinical. The presence of **schistocytes (broken RBCs) on peripheral smear** (see Figure 2.7-3) with low platelets and rising creatinine is highly suggestive.
- **Hemolytic-uremic syndrome (HUS)** can present similarly to TTP.
  - **HUS:** > 90% of cases in children caused by O157:H7 Escherichia coli hemorrhagic diarrhea preceding the syndrome. **Characterized by renal failure, hemolytic anemia, and low platelets without neurologic symptoms.** Severe ↑ in creatinine levels are more typical of HUS than of TTP. Schistocytes are seen in both.

A

This patient is experiencing heparin-induced thrombocytopenia (HIT), which occurs 2° to the formation of antibodies that activate platelets. Because HIT can lead to a hypercoagulable state and subsequent thrombotic complications, heparin must be stopped immediately and the patient must be switched to argatroban.

Treatment

First-line therapy for TTP is **plasma exchange.** Steroids can be added to ↓ microthrombus formation. **Platelet transfusion is contraindicated,** as additional platelets are consumed by the disease process, potentially worsening the patient's condition.

IDIOPATHIC THROMBOCYTOPENIC PURPURA

IgG antibodies are formed against the patient's platelets. The platelet–antibody complex is destroyed by the spleen. Bone marrow production of platelets is ↑, with ↑ megakaryocytes in the marrow. The **most common immunologic disorder in women of childbearing age.**

History/Pe

- Patients often feel well with no systemic symptoms. They may have minor mucocutaneous bleeding, easy bruising, petechiae, hematuria, or melena. Generally there is no splenomegaly.
- ITP is associated with a range of conditions, including **lymphoma, leukemia, SLE, HIV infection, and HCV infection.** Can present acutely or as a chronic illness.
  - **Acute:** Abrupt onset of hemorrhagic complications following a viral illness. Commonly affects children 2–6 years of age, with boys and girls affected equally.
  - **Chronic:** Insidious onset of symptoms or incidental thrombocytopenia on corticosteroid-binding globulin (CBC). Affects adults 20–40 years of age; women > men.

Diagnosis

- **Diagnosis of exclusion:** Once other causes of thrombocytopenia have been ruled out, diagnose by Hx and PE, a CBC, and a peripheral blood smear showing normal RBC morphology.
- Bone marrow biopsy would show ↑ megakaryocytes but is done only in atypical cases or patients > 60 years of age.

Treatment

- Platelet count > 30,000 and no bleeding: **No treatment required.**
- Platelet count < 30,000 or clinically significant bleeding symptoms: **Corticosteroids or IVIG.**
- If platelet count fails to improve or bleeding recurs, consider **splenectomy** ± **rituximab** ± thrombopoietin (TPO) receptor agonist to increase platelet production (**romiplostim** or **eltrombopag**).
- In pregnant patients, severe thrombocytopenia may occur in the fetus.

Red Blood Cell Disorders

ANEMIAS

Anemia is a disorder of **low hematocrit and hemoglobin.** Subtypes are classified according to RBC mean corpuscular volume (MCV) and reticulocyte count (see Figure 2.7-4).

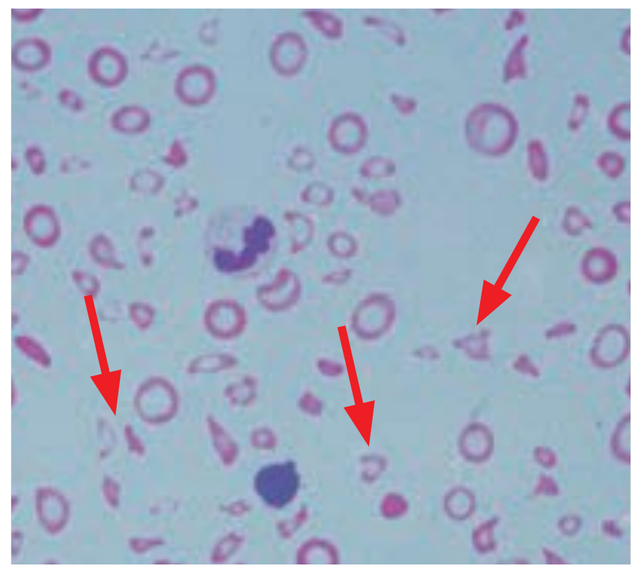


FIGURE 2.7-3. Schistocytes. These fragmented RBCs (arrows) can be seen in microangiopathic hemolytic anemia and in mechanical hemolysis. (Used with permission of Dr. Peter McPhedran, Yale Department of Hematology.)

MNEMONIC

Differential diagnosis of thrombocytopenia—

HIT SHOC

HIT or **H**US
ITP
TTP or **T**reatment (meds)
Splenomegaly
Hereditary (eg, Wiskott-Aldrich syndrome)
Other causes (eg, malignancy)
Chemotherapy

KEY FACT

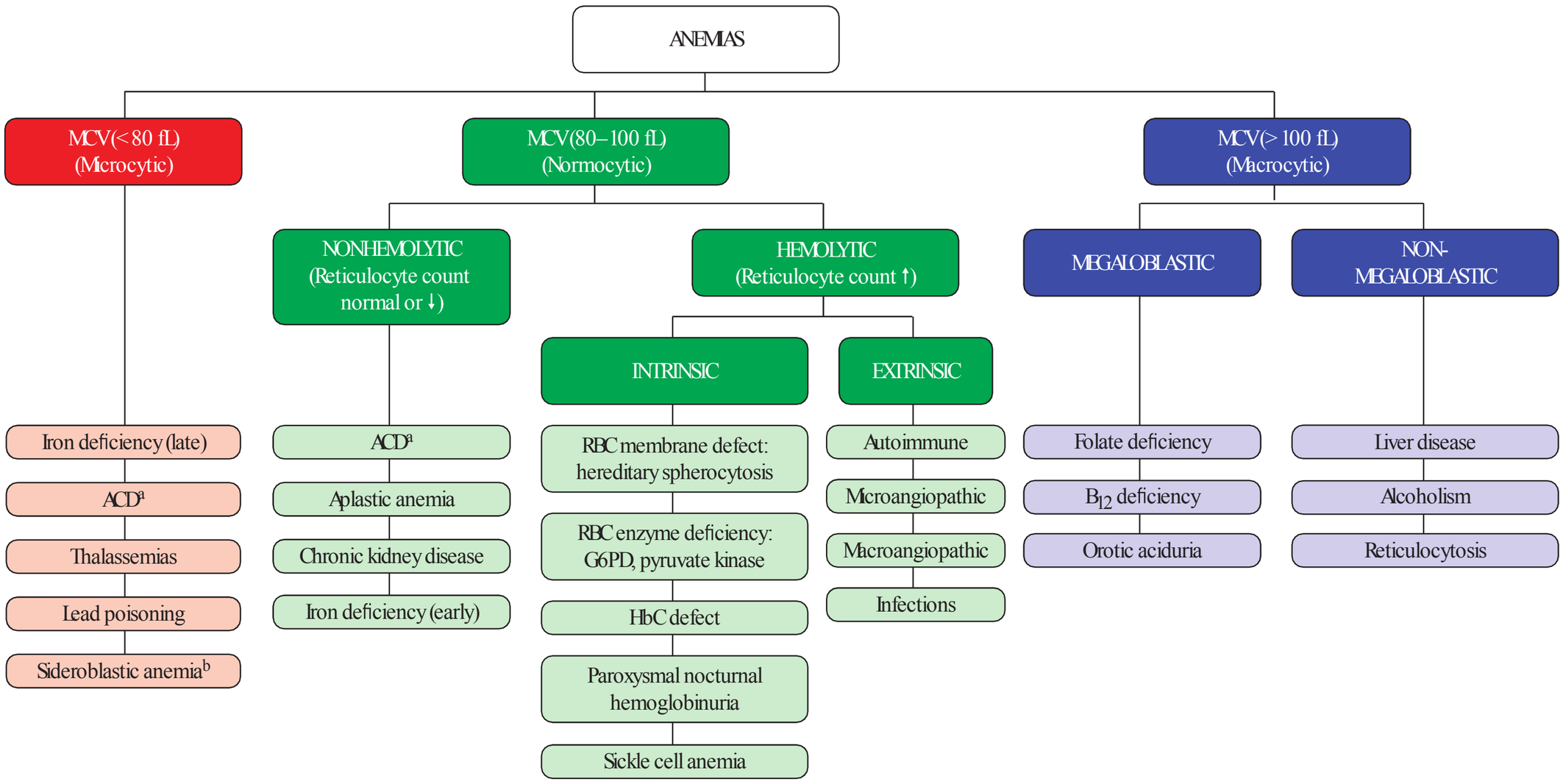
Anti-D (Rh) immunoglobulin and rituximab are second-line therapies for ITP.

KEY FACT

Anti-D (Rh) immunoglobulin and IVIG act as "decoys" so that WBCs will recognize them instead of IgG on platelets.

Q

An 8-year-old girl presents to the ED with 2 days of fever, vomiting, bloody diarrhea, and irritability. She began feeling unwell after attending a classmate's birthday party. Her labs reveal thrombocytopenia, an ↑ creatinine level, and schistocytes. What is the next best step?



[a]ACD and iron deficiency anemia may first present as a normocytic anemia and then progress to a microcytic anemia.
[b]Copper deficiency can cause a microcytic sideroblastic anemia.

FIGURE 2.7-4. Anemia algorithm. ACD = anemia of chronic disease; HbC = hemoglobin C. (Reproduced with permission from Le Tet al. First Aid for the USMLE Step 1 2015. New York, NY: McGraw-Hill; 2015.)

KEY FACT

Iron deficiency anemia in an elderly patient may be due to colorectal cancer and must therefore be evaluated to rule out malignancy.

MNEMONIC

Causes of microcytic anemia—

TICS

Thalassemia
Iron deficien y
Chronic disease
Sideroblastic anemia

A

Hemolytic uremic syndrome (HUS) is the most common cause of acute renal failure in children. Supportive therapy includes IV fluids, BP control, blood transfusion, and, if necessary, dialysis. Antibiotics are not indicated, as they are thought to ↓ expulsion of the toxin and may ↑ toxin from the destruction of bacteria.

Iron Deficiency Anemia (a Microcytic Anemia

Anemia in which iron loss exceeds intake. May occur due to ↑ **demand** (growth phase, pregnancy, EPO therapy) or ↓ **iron** (chronic menorrhagia, GI bleeding, malnutrition/absorption disorders like celiac). **Toddlers, adolescent girls,** and **women of childbearing age** are most commonly affected.

History/Pe

- Symptoms: **Fatigue, dyspnea, tachycardia,** and **pica.**
- If the anemia develops slowly, patients are generally asymptomatic.
- Physical findings: **Glossitis, conjunctival pallor, cheilosis,** and **koilonychia** (**"spoon nails,"** see Figure 2.7-5).

Diagnosis

- Best initial test is a **CBC with iron studies** (see Table 2.7-3). No single value will make the diagnosis, but the constellation of low ferritin (low iron stores), high RBC distribution width (RDW, reflecting high RBC size variation due to poor erythropoiesis), high total iron-binding capacity (TIBC; low iron means lots of empty receptors, so binding capacity is high), and low serum iron point to the correct diagnosis.
- Most accurate test is a bone marrow biopsy, but it is seldom performed.
- Peripheral blood smear shows **hypochromic and microcytic RBCs** (see Figure 2.7-6) with a **low reticulocyte count.**

Treatment

- **Replace iron orally for 4–6 months.** Oral iron sulfate may lead to nausea, constipation, diarrhea, and abdominal pain. Antacids may interfere with iron absorption.

TABLE 2.7-3. Iron Deficiency Anemia vs Anemia of Chronic Disease

	Iron deficiency	Chronic disease	Both/Mixed disease
Serum iron	↓	↓	↓
TIBC or transferrin	↑	↓	Normal/↑
Ferritin	↓	↑	Normal/↓
Serum transferrin receptor	↑	Normal	Normal/↑
RDW	↑	Normal	Normal/↑

- IV iron dextran can be administered but is associated with a small risk of serious side effects, including **anaphylaxis.** Iron sucrose may have a lower risk of allergy.

Anemia of Chronic Inflammation/Diseas

To limit bacterial proliferation, the body "hides" its iron in situations of chronic inflammation such as infection, malignancy, RA, or SLE. This results in a micro- or normocytic anemia with **high levels of iron storage in the form of ferritin,** but low serum iron (see Table 2.7-3).

Sideroblastic Anemia

A microcytic anemia due to defects in heme metabolism that can be hereditary or acquired (common causes include **alcohol, lead poisoning, chloramphenicol, INH,** and malignancy). It presents with a low hemoglobin, **elevated serum iron,** basophilic stippling (in lead poisoning), and ringed sideroblasts on a smear (see Figure 2.7-7).

Megaloblastic Anemia (a Macrocytic Anemia)

Impaired DNA synthesis secondary to **vitamin B_{12} (cobalamin)** or **folate deficiency** leads to megaloblastic anemia. B_{12} deficiency is due to intestinal malabsorption, traditionally from **pernicious anemia** (autoimmune destruction of parietal cells, which produce the intrinsic factor needed for cobalamin absorption) or low dietary intake (vegetarians). Folate deficiency results from alcoholism, low dietary folate, or malabsorption. **Drugs that interfere with DNA synthesis,** including chemotherapeutic agents (methotrexate, 6-mercaptopurine), may lead to megaloblastic anemia.

History/Pe

- Presents with **fatigue, pallor, diarrhea, loss of appetite,** and **headaches.**
- B_{12} deficiency affects the nervous system. Patients may develop a **demyelinating disorder** and present with **subacute combined degeneration of the cord.**
- Patients with **GI disorders are prone to B_{12} deficiency:** Crohn disease, celiac disease, gastrectomy, gastric bypass, pancreatic insufficiency.

Diagnosis

- Best initial test: CBC with smear showing RBCs with an **elevated MCV** and **hypersegmented (six or more lobes) neutrophils** (see Figure 2.7-8).



FIGURE 2.7-5. Koilonychia (spoon nails). The fingernail plate is concave. (Reproduced with permission from Wolff K et al. Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology. New York, NY: McGraw-Hill; 2013.)

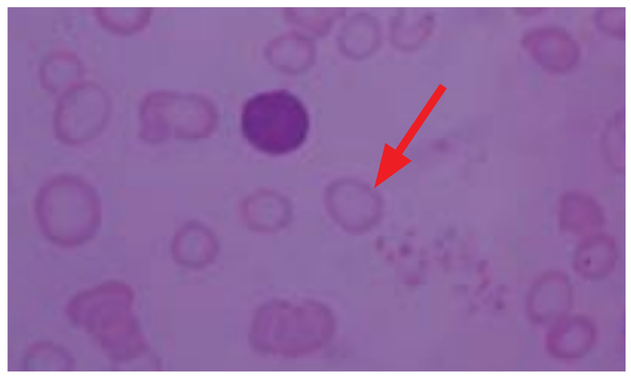
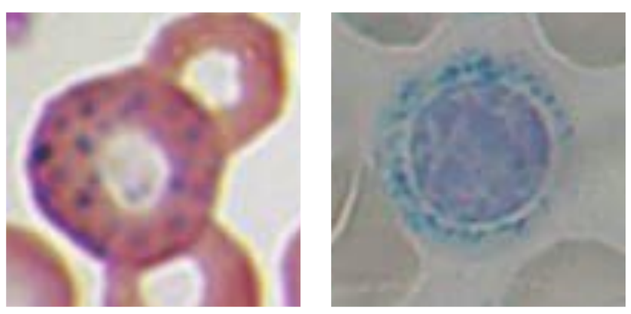


FIGURE 2.7-6. Iron deficiency anemia. Note the microcytic, hypochromic RBCs ("doughnut cells") with enlarged areas of central pallor (arrow). (Used with permission of Dr. Peter McPhedran, Yale Department of Hematology.)



A B

FIGURE 2.7-7. Pathogenic RBC forms. (A) Basophilic stippling. **(B)** Ringed sideroblasts. (Part A reproduced with permission from van Dijk HA, Fred HL. Images of memorable cases: case 81. Connexions Web site. December 3, 2008. Part B used with permission of Paulo Henrique Orlandi Mourao.)

Q

A 49-year-old man comes into the clinic complaining of "tiredness" over the last several months. His past medical history is significant for hypertension, diabetes mellitus, and alcohol abuse. A CBC reveals a low hemoglobin and an MCV of 115. What is the most likely cause of his anemia?

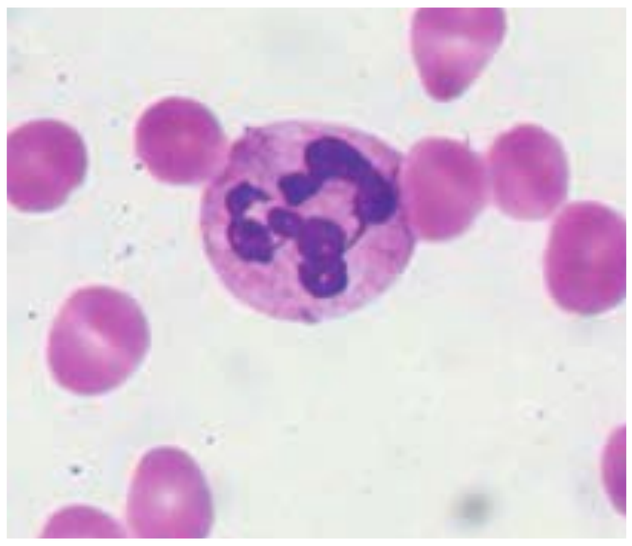


FIGURE 2.7-8. Hypersegmentation. The nucleus of this hypersegmented neutrophil has six lobes (six or more nuclear lobes are required). This is a characteristic finding of megaloblastic anemia. (Used with permission from Dr. Ed Uthman.)

KEY FACT

Subacute combined degeneration of the cord seen in B_{12} deficiency presents as peripheral neuropathy, vibration and proprioception dysfunction, dementia, and spasticity.

KEY FACT

B_{12} deficiency can be due to infection by a tapeworm, Diphyllobothrium latum. Folate deficiency can occur secondary to chronic phenytoin use, causing malabsorption.

KEY FACT

Pernicious anemia increases the risk of **gastric cancer** and is the most common cause of B_{12} deficiency in Europeans.

A

The patient has a **megaloblastic anemia** caused by either a **B_{12}** or **folate deficiency.** His history of alcohol dependence strongly suggests **folate deficiency,** as that is the most common cause of megaloblastic anemia in alcoholics.

- Serum vitamin levels are poorly diagnostic and are used with adjunctive tests, including methylmalonic acid (MMA) and homocysteine levels:
  - B_{12} deficiency: ↑ MMA and ↑ homocysteine.
  - Folate deficiency: **Normal MMA** and ↑ homocysteine.
- Bone marrow sample reveals **giant neutrophils** and **hypersegmented mature neutrophils.**
- The **Schilling test** measures the absorption of cobalamin via ingestion of radiolabeled cobalamin with and without intrinsic factor. This test is rarely performed, but its interpretation is tested. The patient is given an unlabeled B_{12} IM shot to saturate B_{12} receptors in the liver and an oral challenge of radiolabeled B_{12}. The radiolabeled B_{12} will pass into the urine if properly absorbed, as the liver's B_{12} receptors will be saturated from the IM dose.
  - **Radiolabeled B_{12} in urine:** Dietary B_{12} deficiency.
  - **No radiolabeled B_{12} in urine:** Consider pernicious anemia, bacterial overgrowth, or pancreatic enzyme deficiency; test the hypothesis with the addition of intrinsic factor, antibiotics, or pancreatic enzymes to radiolabeled B_{12}.

Treatment

Correct the underlying cause of the anemia.

Hemolytic Anemia (a Normocytic Anemia)

Occurs when bone marrow production is unable to compensate for ↑ destruction of circulating blood cells. Etiologies include the following:

- **Glucose 6-phosphate dehydrogenase (G6PD) deficiency, paroxysmal nocturnal hemoglobinuria (PNH), spherocytosis** (Figure 2.7-9), **sickle cell disease,** and **autoimmune anemia** will be discussed separately below, but the general principles in this section will apply.
- **Microangiopathic hemolytic anemia:** TTP, HUS, DIC.
- **Mechanical hemolysis:** Associated with **mechanical heart valves.**
- **Other:** Malaria, hypersplenism.

History/Pe

- Present with **pallor, fatigue, tachycardia,** and **tachypnea.**
- Patients are often **jaundiced,** with ↑ reticulocyte count, indirect bilirubin, and LDH, and a ↓ haptoglobin. Urine is dark with **hemoglobinuria,** and there is ↑ excretion of urinary and fecal urobilinogen.

Diagnosis

Clinical. **↑ LDH, ↑ indirect bilirubin, ↑ reticulocyte count, and ↓ haptoglobin** are commonly seen.

Treatment

Varies with the cause, but often includes **corticosteroids** to address immunologic causes and **iron supplementation** to replace losses. Splenectomy or transfusions are helpful in severe cases.

G6PD Deficienc

X-linked recessive defect in G6PD, leaving RBCs susceptible to hemolytic anemia following oxidant stress. Patients are often of Mediterranean or African descent, presenting with episodic dark urine and jaundice. Common triggers include: sulfa drugs (TMP-SMX), antimalarials (quinines), infections, **fava beans.** Best initial test is a CBC with smear showing hemolytic ane-

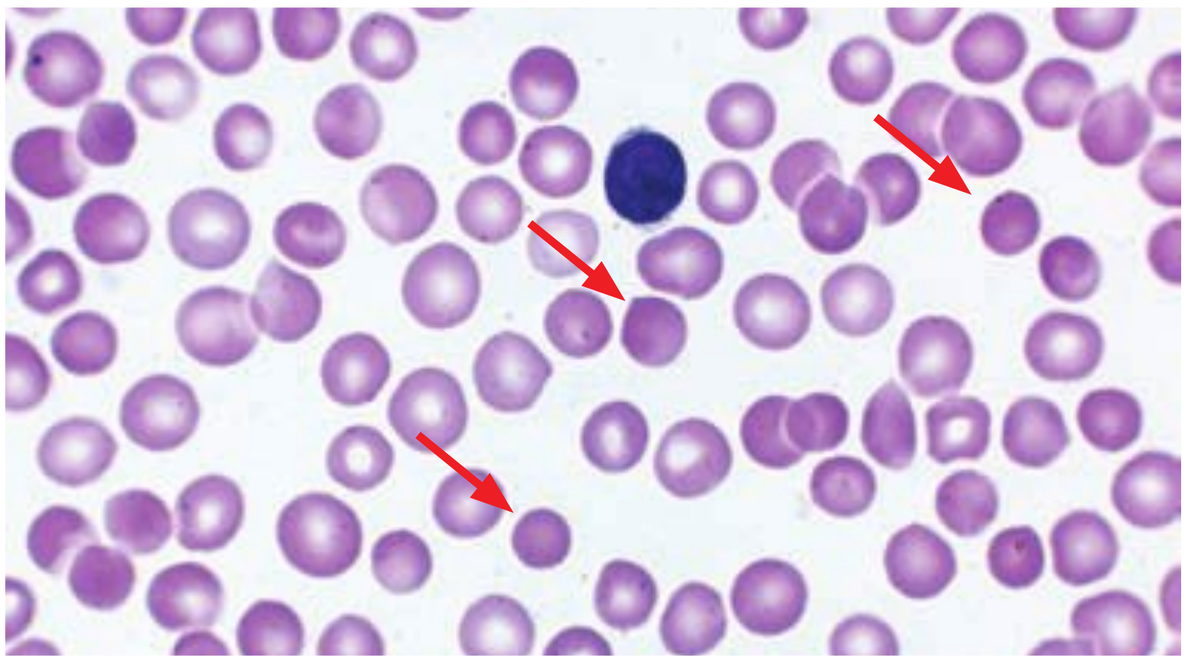


FIGURE 2.7-9. Spherocytes. These RBCs (arrows) lack areas of central pallor. Spherocytes are seen in autoimmune hemolysis and in hereditary spherocytosis. (Reproduced with permission from Bun HF, Aster JC. Pathophysiology of Blood Disorders. New York, NY: McGraw Hill; 2011.)

mia with **bite cells** and **Heinz bodies.** Most accurate test is a G6PD level **a month after an episode.** Patients should avoid triggers.

Paroxysmal Nocturnal Hemoglobinuria

CD55/CD59 proteins found on the surface of RBCs protect them from complement-mediated hemolysis. **PNH is a deficiency in GPI-anchor molecules that keep CD55/CD59 attached to cells, resulting in hemolysis by complement.** PNH can manifest as anemia, dark urine, venous thrombosis, and abdominal pain. **Most accurate diagnostic test is CD55/CD59 absence via flow cytometry.**

Hereditary Spherocytosis

Autosomal dominant defect or deficiency in **spectrin or ankyrin,** an RBC membrane protein resulting in a loss of RBC membrane surface area → RBCs are forced to take spherical shapes and are subsequently destroyed by the spleen. Clinically presents as an extravascular hemolytic anemia. Best initial test is a CBC with smear showing **spherocytes** (see Figure 2.7-9). Most accurate diagnostic test is an **osmotic fragility test.** Manage with a **splenectomy.**

Sickle Cell Disease

An **autosomal recessive** disorder caused by a mutation of adult hemoglobin (the β-chain has Glu replaced by Val). Signs and symptoms are due to **↓ RBC survival** and a tendency of sickled cells to aggregate and cause **vaso-occlusion.**

History/Pe

- May first present with dactylitis in childhood. Lifelong hemolysis results in **anemia, jaundice, pigmented cholelithiasis, ↑ CO (murmur, eventual CHF),** and **delayed growth.**
- Vaso-occlusion leads to ischemic organ damage, especially **splenic infarction,** which predisposes to pneumococcal sepsis and acute chest syndrome (pneumonia and/or pulmonary infarction; see Figure 2.7-10). These crises can also cause avascular hip necrosis, priapism, and strokes. Common triggers include cold temperatures, dehydration, and infection.

KEY FACT

A classic presentation of G6PD deficiency is a black male patient presenting with fatigue, dark urine and SOB after taking TMP-SMX for a cold.

KEY FACT

Causes of oxidative stress in G6PD deficiency include infection, metabolic acidosis, fava beans, antimalarials, dapsone, sulfonamides, and nitrofurantoin.

KEY FACT

Patients who had a splenectomy for any reason are at an increased lifelong risk of sepsis and thus require pneumococcal, meningococcal, and Haemophilus vaccinations before the operation.

KEY FACT

Sickling occurs with dehydration, deoxygenation, and at high altitude. If it happens in the vasa rectae (vessels supplying the inner medulla of the kidneys), sickle cell patients can have ↓ ability to concentrate urine, presenting as polyuria or nocturia.



FIGURE 2.7-10. Acute chest syndrome. Frontal CXR of a 19-year-old woman with sickle cell disease and acute chest pain. Note the bilateral lower and midlung opacities and mild cardiomegaly. (Reproduced with permission from USMLE-Rx.com.)

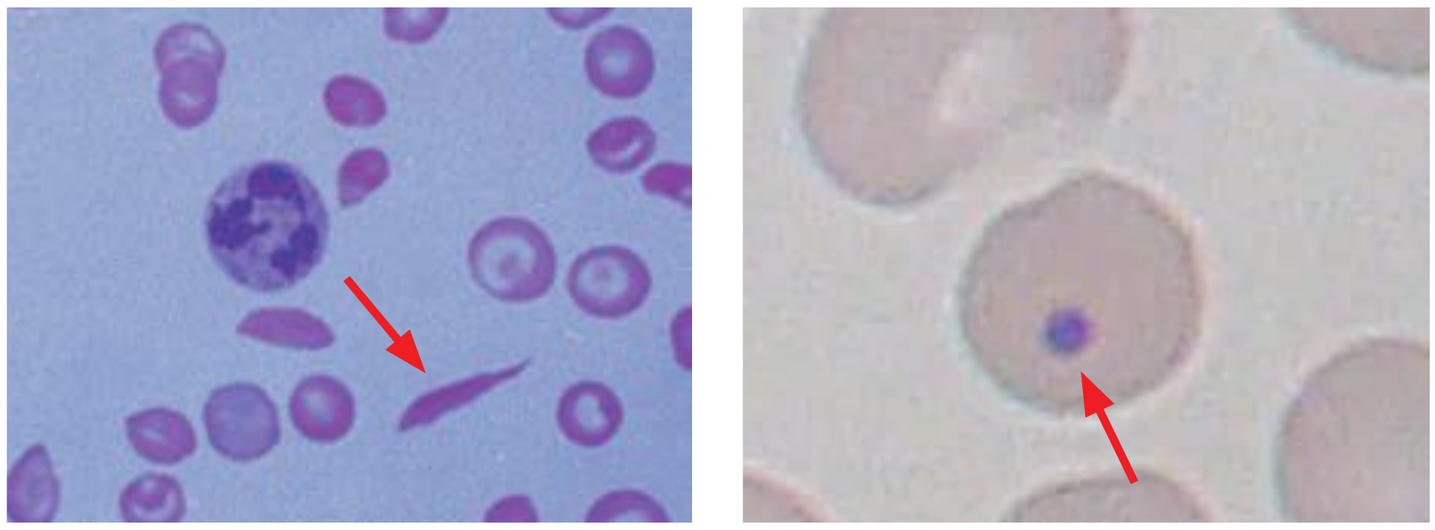
KEY FACT

The most common cause of osteomyelitis in patients with SCD is Salmonella, followed by S aureus. They are also at ↑ risk for avascular necrosis of the hip.

- Other potential complications include splenic sequestration (sudden pooling of blood into the spleen resulting in hypovolemia) and aplastic crisis (2° to infection with viruses such as parvovirus B19). These complications both present with ↓ hematocrit but are distinguished clinically by ↓ platelets in aplastic crisis (2° to bone marrow involvement) and normal to ↑ platelets in splenic sequestration.

Diagnosis

Fastest initial test is CBC with smear **showing sickle cells** and Howell-Jolly bodies (see Figure 2.7-11A, B). Most accurate test is hemoglobin electrophoresis.



A B

FIGURE 2.7-11. Sickle cell disease. (A) Sickle-shaped RBCs (arrow) are almost always seen on blood smear, regardless of whether the patient is having a sickle cell crisis. **(B)** Howell-Jolly bodies, which suggest functional hyposplenia or asplenia. (Part A used with permission of Dr. Peter McPhedran, Yale Department of Hematology. Part B used with permission of Paulo Henrique Orlandi Mourao and Mikael Häggström.)

Treatment

- Treat with **hydroxyurea,** which stimulates the **production of fetal hemoglobin** (hydroxyurea is teratogenic, so it is contraindicated in pregnancy).
- If hydroxyurea does not prove effective, chronic transfusion therapy, which carries the risk of iron overload, can be tried.
- **Health maintenance includes treating cholelithiasis with cholecystectomy, chronic folate supplementation, pneumococcal vaccination, and penicillin in patients < 5 years of age.**
- Vaso-occlusive crises (VOCs) must be treated with adequate pain management, O_2 therapy, IV fluid rehydration, and antibiotics (if infection is suspected to be the trigger).
- If there is concern of a VOC progressing to acute chest syndrome, initiate aggressive hydration and incentive spirometry, and keep the sickle variant < 40%. This can be done with simple transfusions or, if necessary, exchange transfusion in an ICU setting.

Autoimmune Hemolytic Anemia

Autoantibodies against RBC membrane destroy blood cells, causing hemolysis. Two types: warm [Ig**G,** associated with SLE, chronic lymphocytic leukemia (CLL), drugs] and cold (Ig**M,** associated with Mycoplasma pneumonia, mononucleosis). Presents as a hemolytic anemia. Diagnose with a **direct Coombs test** (see Figure 2.7-12). If AIHA is mild, no treatment is necessary. Severe warm AIHA is treated with **steroids.** Severe cold AIHA is managed by avoiding exposure to cold ± rituximab (anti-CD20 antibody).

Aplastic Anemia

Failure of blood cell production due to **destruction of bone marrow cells.** It may be hereditary, as in **Fanconi anemia;** may have an **autoimmune** or

KEY FACT

The indirect Coombs test detects antibodies to RBCs in the patient's serum. The direct Coombs test detects sensitized erythrocytes.

KEY FACT

Both AIHA and hereditary spherocytosis can present with spherocytes and positive osmotic fragility tests, but only AIHA will have a ⊕ **direct Coombs test.**

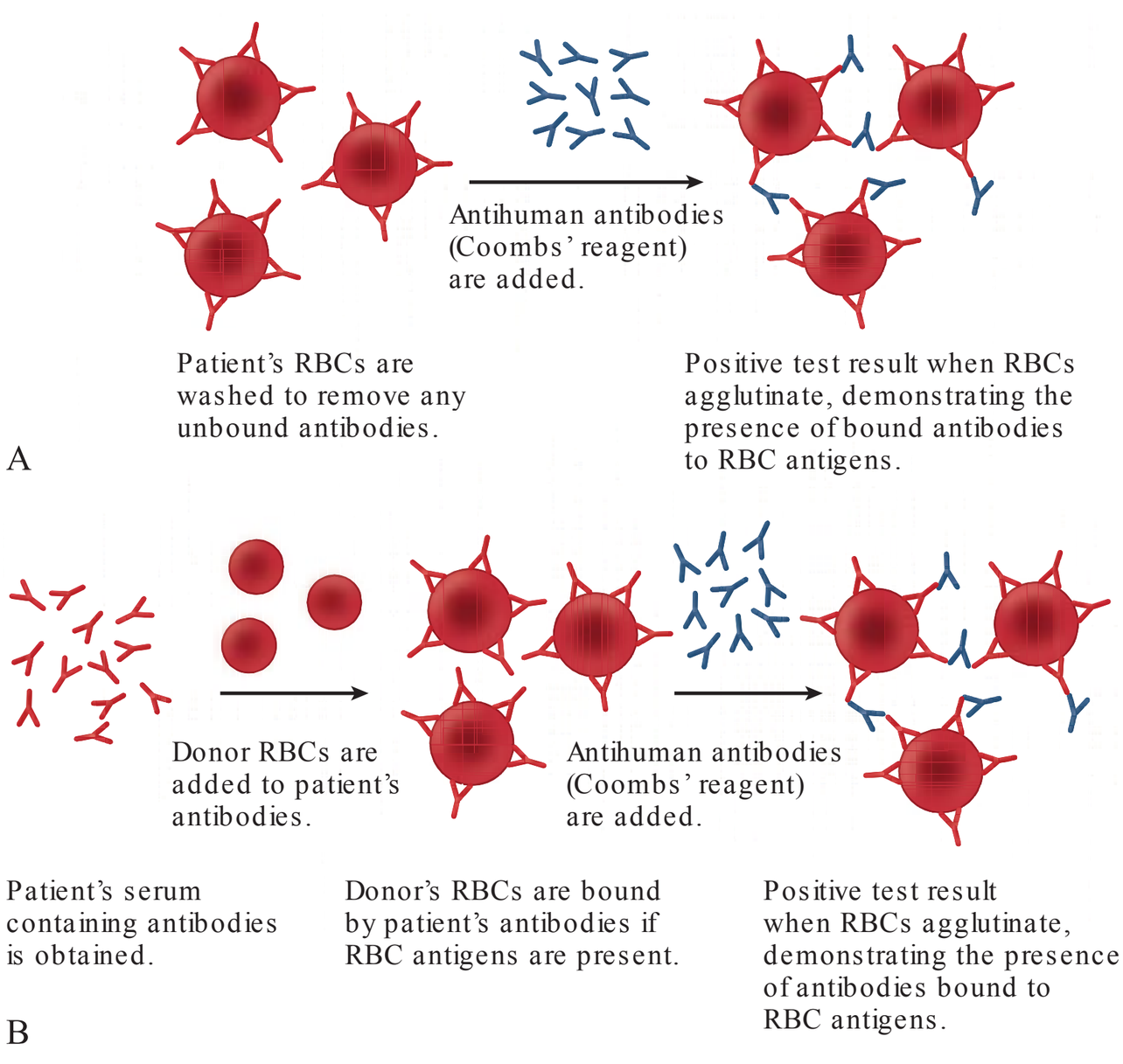


FIGURE 2.7-12. Direct (A) and indirect (B) Coombs tests.

KEY FACT

Patients with Fanconi anemia can be identified on physical examination by café-au-lait spots, short stature, and radial/thumb hypoplasia/aplasia.

a **viral** etiology (HIV, parvovirus B19); or may result from exposure to **toxins** (cleaning solvents), **radiation,** or **drugs** (sulfa, chloramphenicol, propylthiouracil, methimazole).

History/Pe

Patients are **pancytopenic,** with symptoms resulting from a lack of RBCs, WBCs, and platelets: **pallor, weakness, a tendency to infection, petechiae, bruising, and bleeding.**

Diagnosis

Diagnosed by clinical presentation and CBC. Most accurate test is a **bone marrow biopsy** revealing hypocellularity and space occupied by fat.

Treatment

Blood transfusion and stem cell transplantation to replace absent cells. In severe cases or in patients without a stem cell donor, immunosuppress with cyclosporin A and antithymocyte globulin to prevent autoimmune marrow destruction. **Infections** should be treated aggressively.

THALASSEMIAS

Hereditary disorders involving ↓ or absent production of normal globin chains of hemoglobin. α-Thalassemia is caused by a mutation of one or more of the four genes that encode α-hemoglobin; β-thalassemia results from a mutation of one or both of the two genes encoding β-hemoglobin.

History/Pe

Thalassemia is most common among people of **African, Middle Eastern,** and **Asian descent.** Disease presentation varies with the number of genes missing (see Table 2.7-4). A typical case can be an asymptomatic or fatigued individual with a microcytic anemia and **normal iron studies.**

Diagnosis

Diagnosed by **hemoglobin electrophoresis** (normal in α trait, α silent carrier) and DNA studies.

Treatment

- Most patients do not require treatment.
- Those with β-thalassemia major and hemoglobin H disease are often transfusion dependent and require iron chelators (deferoxamine) to prevent overload.

POLYCYTHEMIAS

Erythrocytosis (an abnormal elevation of hematocrit) may be either absolute (↑ RBC production) or relative (↓ plasma volume and hemoconcentration).

History/Pe

- Characterized by ↑ hematocrit, ↓ tissue blood flow and oxygenation, and ↑ cardiac work.
- Patients present with **"hyperviscosity syndrome":** easy bleeding/bruising, blurred vision, neurologic deficits, pruritus after a warm bath, **thrombosis,** CHF, hepatosplenomegaly.

TABLE 2.7-4. Differential Diagnosis of Thalassemias

Subtype	Number of Genes Present	Clinical Features
β-thalassemia major	0/2 β	Patients develop severe microcytic anemia in the first year of life and need chronic transfusions or marrow transplant to survive.
β-thalassemia minor	1/2 β	Patients are asymptomatic, but their cells are microcytic and hypochromic on peripheral smear. Common in the Mediterranean.
Hydrops fetalis	0/4 α	Patients die in utero.
Hemoglobin H disease	1/4 α	Patients have severe hypochromic, microcytic anemia with chronic hemolysis, splenomegaly, jaundice, and cholelithiasis. **The reticulocyte count ↑ to compensate,** and one-third of patients have skeletal changes due to expanded erythropoiesis.
α-thalassemia trait	2/4 α	Patients have low MCV but are usually asymptomatic.
Silent carrier	3/4 α	Patients have no signs or symptoms of disease.

Q

A 30-year-old man from Greece comes to your office complaining of chronic fatigue. He has no significant past medical history and is on no medications. A CBC shows hemoglobin of 10.4, MCV of 71. You start him on oral iron supplements and see him back in 4 weeks with no change in the CBC. What is the most likely diagnosis?

- Absolute erythrocytosis is associated with hypoxia (lung disease, smoking, high altitudes, or a poor intrauterine environment), neoplasia (EPO-producing tumors), or **polycythemia vera (PCV).**
  - PCV results from **clonal proliferation of a pluripotent marrow stem cell due to a** JAK2 **mutation.** All marrow cell lines ↑ but RBCs are most significantly affected.
  - This blood disorder most commonly affects older individuals.
- Relative erythrocytosis is associated with hypovolemia: diuresis, gastroenteritis, burns.

Diagnosis

- PCV: Best initial test is a CBC showing **elevated RBCs/WBCs/platelets** with an ABG and EPO level. ↓ **EPO,** normal O_2, and **HCT > 60%** suggest PCV.
- Most accurate test is the JAK2 **mutation.**
- Relative erythrocytosis also has an ↑ HCT, but **EPO is normal or** ↑ and O_2 is often ↓ compared to PCV.

Treatment

- PCV: Phlebotomy and aspirin provide symptom relief and prevent thrombosis. **Hydroxyurea and IFN** reduce cell counts.
- Relative erythrocytosis: Address the underlying cause and treat symptoms with phlebotomy.

KEY FACT

Premedication with acetaminophen and diphenhydramine is sometimes used to prevent minor transfusion reactions.

KEY FACT

Hemoglobinuria in hemolytic transfusion reaction may lead to acute tubular necrosis and subsequent renal failure.

KEY FACT

Heme is necessary for the production of hemoglobin, myoglobin, and cytochrome molecules.

A

The most likely diagnosis is β-thalassemia minor. Recognize that this patient has a **microcytic** anemia that did not respond to iron supplements (probably has normal iron studies) and is from the Mediterranean.

KEY FACT

The telltale sign of porphyria is pink urine. The classic case involves a college student who consumes alcohol and barbiturates at a party and then has an acute episode of abdominal pain and brown urine the next day.

KEY FACT

Symptoms of acute intermittent porphyria **(5 P's):**

- **P**ainful abdomen
- **P**ort wine–colored urine
- **P**olyneuropathy
- **P**sychological disturbances
- **P**recipitated by drugs (eg, cytochrome P450 inducers), alcohol, starvation

BLOOD TRANSFUSION REACTIONS

Transfusions are generally safe but may result in adverse reactions (see Table 2.7-5). Febrile nonhemolytic and allergic reactions are the most common, occurring in 3–4% of all transfusions.

PORPHYRIA

Group of inherited disorders with abnormalities in heme production that lead to an **accumulation of porphyrins.** They include acute intermittent porphyria, erythropoietic porphyria, and porphyria cutanea tarda (most common). Lead poisoning inhibits heme synthesis enzymes and can **produce a porphyria-like** disorder.

History/Pe

- In general, porphyrias are characterized by a combination of **photodermatitis, neuropsychiatric complaints,** and **visceral complaints** that take the form of **colicky abdominal pain and seizures.**
- Physical examination reveals **tachycardia, skin erythema, blisters, areflexia,** and a nonspecific abdominal examination.
- Patients with the erythropoietic form present with **hemolytic anemia.** Acute attacks are associated with stimulants of ↑ heme synthesis such as fasting or chemical exposures; well-known triggers are alcohol, barbiturates, and OCPs. Urine may appear pink or brown after an attack. Patients may have a ⊕ family history.

Diagnosis

- Best initial test is urine and plasma porphyrin levels.
- Most accurate test is specific mutation or enzyme analysis.

Treatment

- Avoidance of triggers and symptomatic treatment during acute attacks.
- High doses of **glucose** ↓ heme synthesis during attacks (provides ⊖ feedback to the heme synthetic pathway).

TABLE 2.7-5. Transfusion Reactions

Variable	Febrile nonhemolytic reaction	allergic reaction	hemolytic transfusion reaction
Mechanism	**Cytokine formation** during storage of blood.	Antibody formation **against donor proteins,** usually after receiving plasma-containing product.	Preformed (acute) or formed (delayed) recipient antibodies **against donor erythrocytes.** Due to ABO mismatch or Rh and Duffy a tigens.
Presentation	Fever, chills, rigors, and malaise **1–6 hours after transfusion.**	Prominent urticaria.	Fevers, chills, nausea, flushin , burning at the IV site, tachycardia, hypotension **during or shortly after the transfusion.**
Treatment	Stop the transfusion and give acetaminophen.	Give antihistamines. If severe reaction, stop the transfusion and give epinephrine.	Stop the transfusion immediately! Give vigorous IV fluids and mai tain good urine output.

White Blood Cell Disorders

LEUKEMIAS

Malignant proliferations of hematopoietic cells, categorized by the type of cell involved and their level of differentiation.

Acute Leukemias

Acute myelogenous and lymphocytic leukemias are clonal disorders of early hematopoietic stem cells (blasts) resulting in unregulated growth and differentiation of WBCs in bone marrow. As the bone marrow becomes overwhelmed, anemia (↓ RBCs), infection (↓ mature WBCs), and hemorrhage (↓ platelets) result.

History/Pe

- AML and acute lymphocytic leukemia (ALL) affect children as well as adults. **ALL is the most common childhood malignancy.**
- Rapid onset and progression. Patients present with signs and symptoms of anemia (pallor, fatigue), thrombocytopenia **(petechiae, purpura, bleeding),** infections (ineffective and immature WBCs) and **DIC** (seen in AML). Medullary expansion into the periosteum may lead to **bone pain** (common in ALL).
- Exam may show **hepatosplenomegaly** and **swollen/bleeding gums** from leukemic infiltration and ↓ platelets. Leukemic cells also infiltrate the skin and CNS.

Diagnosis

- Best initial test: CBC with smear showing blast cells.
- Most accurate test is a bone marrow biopsy with flow cytometry to classify leukemia type.
- Marrow that is infiltrated with blast cells is consistent with leukemia. **In AML, the leukemic cells are myeloblasts; in ALL they are lymphoblasts.** These cells can be distinguished by morphology (see Figure 2.7-14), cytogenetics, and immunophenotyping (see Table 2.7-6).
- The WBC count can be elevated, but the cells are dysfunctional, and patients may be neutropenic with a **history of frequent infection.** If the WBC count in AML is very high (> 100,000/mm^3), there is a risk of **leukostasis** (blasts occluding the microcirculation, leading to pulmonary edema, CNS symptoms, ischemic injury, and DIC).

Treatment

- In general, ALL and AML are treated with **chemotherapy.** Patients with a leukemia subtype of unfavorable genetics may be candidates for bone marrow transplantation.
- To prevent **tumor lysis syndrome** (hyperuricemia, renal insufficiency, as blasts are destroyed by chemotherapy), patients should be well hydrated. If WBC counts are ↑, they may also be started on **allopurinol** or **rasburicase** (often used in the pediatric population).
- Leukostasis syndrome may be treated with hydroxyurea ± leukapheresis to ↓ WBC count.
- Indicators of poor prognosis:
  - **ALL:** Age < 1 or > 10 years; an ↑ in WBC count to > 50,000/mm^3; presence of the Philadelphia chromosome t(9,22) (associated with B-cell cancer); CNS involvement at diagnosis.
  - **AML:** Age > 60 years; elevated LDH; poor-risk or complex karyotype.

KEY FACT

A characteristic sign for AML subtype M3 (APL) is the **Auer rod** (see Figure 2.7-13), although Auer rods can be seen in other AML subtypes.

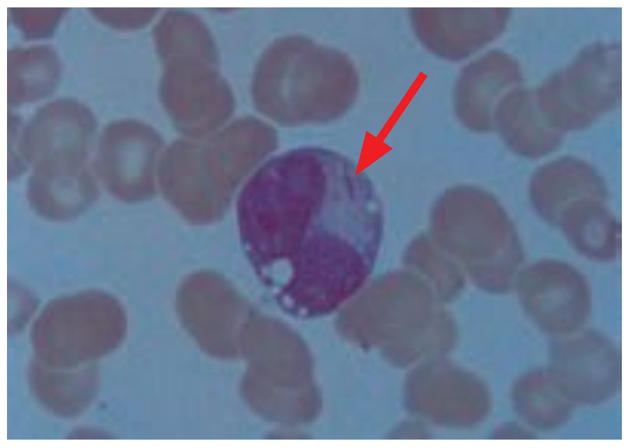


FIGURE 2.7-13. Auer rod in AML. The red rod-shaped structure (arrow) in the cytoplasm of the myeloblast is pathognomonic. (Used with permission of Peter McPhedran, MD, Yale Department of Hematology.)

KEY FACT

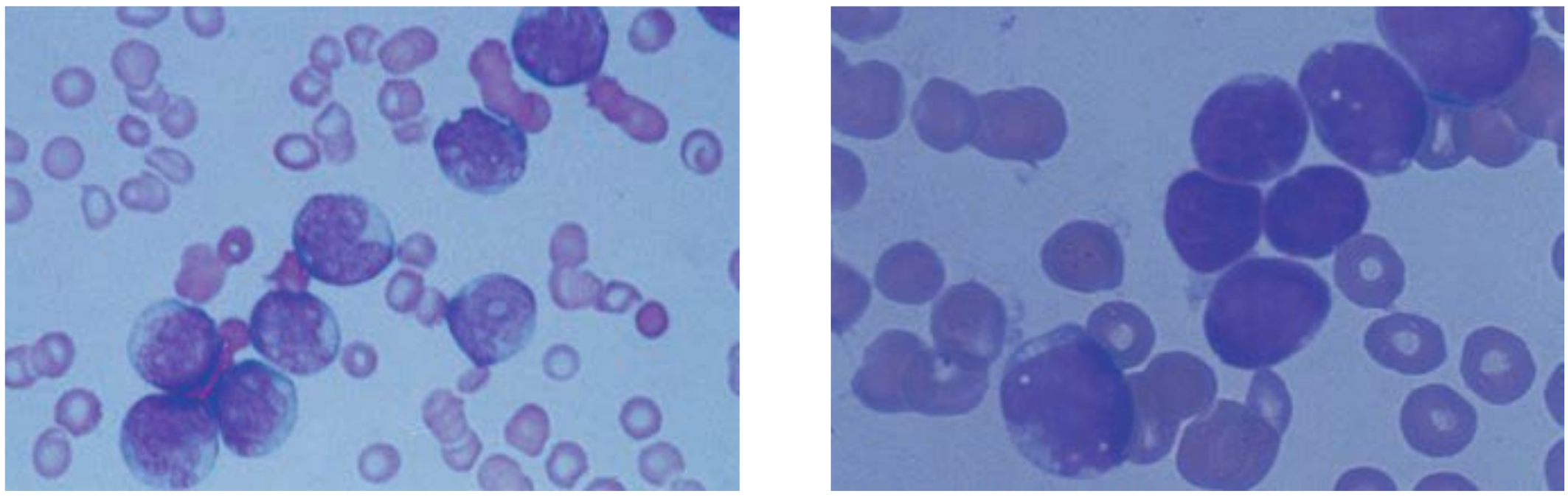
Eighty-five percent of children with ALL achieve complete remission with chemotherapy.

Q 1

A 35-year-old man is airlifted to the ED after a motor vehicle accident. He requires multiple transfusions, which stabilize his BP and hemoglobin. The following morning he is transferred to his hospital room, where he begins to complain of numbness in his fingers. A prolonged QT interval is noted on an ECG. What is the most likely diagnosis?

Q 2

A 15-year-old girl sees her pediatrician after being diagnosed with mononucleosis. Her WBC count returns at 56,000/mm^3. The physician orders a leukocyte alkaline phosphatase (LAP) to distinguish between a leukemoid reaction and a hematologic malignancy. What is the expected result in a leukemoid reaction?



A B

FIGURE 2.7-14. AML vs ALL on peripheral smear. (A) AML. Large, uniform myeloblasts with round or kidney-shaped nuclei and prominent nucleoli are characteristic. **(B) ALL.** Peripheral blood smear reveals numerous large, uniform lymphoblasts, which are large cells with a high nuclear-to-cytoplasmic ratio. Some lymphoblasts have visible clefts in their nuclei. (Used with permission of Dr. Peter McPhedran, Yale Department of Hematology.)

Chronic Lymphocytic Leukemia

A malignant, clonal proliferation of **functionally incompetent lymphocytes** that accumulate in the bone marrow, peripheral blood, lymph nodes, spleen, and liver. The most common type of leukemia. Almost all cases involve **well-differentiated B lymphocytes.** Primarily affects **older adults** (median age 65); the male-to-female ratio is 2:1.

History/Pe

Often asymptomatic; patients present with **fatigue, malaise, and infection.** Common physical findings are **lymphadenopathy and splenomegaly.**

Diagnosis

- Best initial test: CBC with differential and smear showing **lymphocytosis** (NK cells, T cells, or B cells > 5000/mm^3) and **characteristic smudge cells** (fragile leukemia cells crushed by the slide). See Figure 2.7-15.
- Most accurate test: Flow cytometry showing the CD5 marker on B cells (normally found on T cells).

1 A

This patient presents with symptoms of **hypocalcemia** following multiple blood transfusions. Blood products often contain **citrate,** which binds to serum calcium, leading to hypocalcemia, which can cause prolonged QT intervals.

TABLE 2.7-6. Myeloblasts vs Lymphoblasts

Variable	Myeloblast	Lymphoblast
Size	Larger (2–4 times RBC)	Smaller (1.5–3.0 times RBC)
Amount of cytoplasm	More	Less
Nucleoli	Conspicuous	Inconspicuous
Granules	Common, fin	Uncommon, coarse
Auer rods	Present in 50% of cases (see Figure 2.7-13)	Absent
Myeloperoxidase	⊕	⊖

2 A

LAP would be ↑. Hematologic malignancies, in contrast, have ↓ LAP values.

- **Granulocytopenia, anemia, and thrombocytopenia** are common as leukemic cells infiltrate bone marrow. Abnormal function by the leukemic cells leads to **hypogammaglobulinemia.**
- Bone marrow biopsy is rarely required for diagnosis but may provide prognostic information.

Treatment

- Treatment is chemotherapy with fludarabine and chlorambucil.
- Treatment, however, is palliative and is **often withheld until patients are symptomatic:** recurrent infection, severe lymphadenopathy or splenomegaly, **anemia or thrombocytopenia (worst prognosis).**
- Although CLL is not curable, long disease-free intervals may be achieved with adequate treatment of symptoms. The clinical stage correlates with expected survival.

Chronic Myelogenous Leukemia

Clonal expansion of myeloid progenitor cells, leading to leukocytosis with excess granulocytes and basophils and sometimes ↑ erythrocytes and platelets as well. To truly be CML, the **BCR-ABL** translocation must be present. In > 90% of patients, this is reflected by the **Philadelphia chromosome t(9,22).** CML primarily affects **middle-aged** patients.

History/Pe

- Many patients are asymptomatic at diagnosis. Typical signs and symptoms are those of **anemia.**
- Patients can have **splenomegaly** with LUQ pain and early satiety. **Constitutional symptoms** of weight loss, anorexia, fever, and chills may also be seen.
- Patients with CML go through three disease phases:
- **Chronic:** Without treatment this phase typically lasts 3.5–5.0 years. Infection and bleeding complications are rare.
- **Accelerated:** A transition toward blast crisis, with an ↑ in peripheral and bone marrow blood counts. Should be suspected when the differential shows an abrupt ↑ in basophils and thrombocytopenia (platelet count < 100,000/mm^3).
- **Blast crisis:** A large percentage of untreated CML patients will eventually reach this phase. Resembles acute leukemia; survival is 3–6 months.

Diagnosis

- Most accurate test: Philadelphia chromosome via PCR or FISH analysis showing the t(9,22) translocation, although some cases lack the translocation.
- CBC often shows a **very high WBC count**—often > 100,000/mm^3 at diagnosis, sometimes reaching > 500,000/mm^3. The differential shows granulocytes in all stages of maturation. Rarely, the WBC count will be so elevated as to cause a **hyperviscosity syndrome.**
- CML can be confused clinically with a **leukemoid** reaction (acute inflammatory response to infection with ↑ neutrophils and a left shift). In CML and other hematologic malignancies, **LAP is low** while in leukemoid reactions **LAP is high.**
- LDH, uric acid, and B_{12} levels are also often elevated in CML.

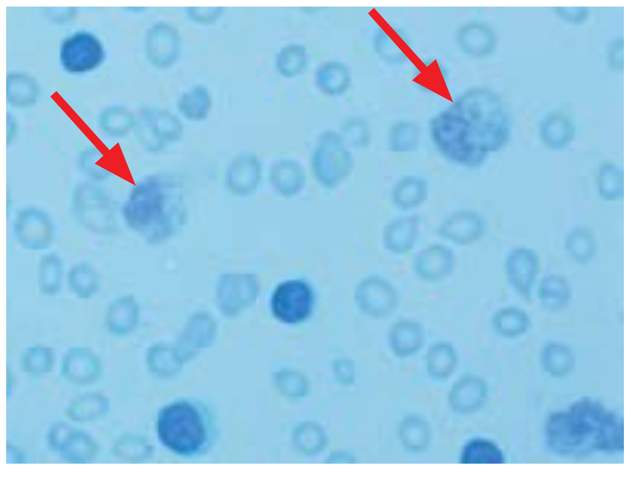


FIGURE 2.7-15. CLL with characteristic smudge cells. The numerous small, mature lymphocytes and smudge cells (arrows; fragile malignant lymphocytes are disrupted during blood smear preparation) are characteristic. (Used with permission of Dr. Peter McPhedran, Yale Department of Hematology.)

KEY FACT

Look for smudge cells to point you toward CLL. Smudge cells result from the coverslip crushing the fragile leukemia cells.

KEY FACT

Likely diagnosis based on age at presentation:

- **ALL:** < 13 years (but can present in any age group)
- **AML:** 13–40 years (but can present in any age group)
- **CML:** 40–60 years
- **CLL:** > 60 years

KEY FACT

A common lab finding of CLL is **lymphocytosis** (elevation of NK, T, or B cells) vs CML, which shows **granulocytosis** (↑ of granulocytes: neutrophils, eosinophils, or basophils).

Q

A 41-year-old man is diagnosed with acute myelogenous leukemia (AML). Fluorescence in situ hybridization (FISH) analysis reveals that he has acute promyelocytic leukemia (APL), FAB subtype M3. What is the preferred therapy for this subtype of AML?

Treatment

- **Chronic:** Treat with imatinib (Gleevec). Young patients are also candidates for allogeneic stem cell transplantation if a matched sibling donor is available.
- **Blast crisis:** Same as that for acute leukemia, or dasatinib plus hematopoietic stem cell transplantation or a clinical trial.

Hairy Cell Leukemia

A malignant disorder of well-differentiated B lymphocytes. HCL is a **rare** disease that accounts for 2% of adult leukemia cases and most commonly affects **older men.**

History/PE

- Typically presents with pancytopenia, bone marrow infiltration, and splenomegaly.
- Patients complain of weakness, fatigue, petechiae, bruising, infection (especially with atypical mycobacteria such as Mycobacterium avium–intracellulare), abdominal pain, early satiety, and weight loss. Symptoms are similar to those of CLL except that patients rarely have lymphadenopathy.

Diagnosis

- Best initial test: CBC with smear showing pathognomonic **"hairy cells"** (mononuclear cells with many cytoplasmic projections, see Figure 2.7-16) that stain with **tartrate-resistant acid phosphatase (TRAP).** Leukopenia can sometimes be seen as well.
- Most accurate test: Flow cytometry identifying the "hairy cells."

Treatment

- First-line therapy is **cladribine.** If left untreated, most patients will develop progressive pancytopenia and splenomegaly eventually requiring therapy.
- Alternative treatment options include splenectomy and IFN-α.
- The median survival without treatment is 5 years.

KEY FACT

Imatinib (Gleevec) is a selective inhibitor of the BCR-ABL tyrosine kinase, the product of the t(9,22) translocation, or Philadelphia chromosome.

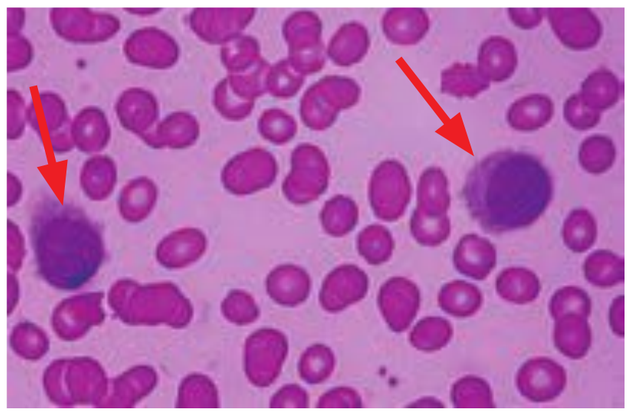


FIGURE 2.7-16. Hairy cell leukemia. Note the hairlike cytoplasmic projections from neoplastic lymphocytes. Villous lymphoma can also have this appearance. (Used with permission of Dr. Peter McPhedran, Yale Department of Hematology.)

LYMPHOMAS

Malignant transformations of lymphoid cells residing primarily in lymphoid tissues, especially the lymph nodes. Classically organized into Hodgkin (HL) and non-Hodgkin (NHL) lymphoma (see Table 2.7-7).

Non-Hodgkin Lymphoma (NHL)

NHL represents a diverse group of mature B and T cell neoplasms. **Most NHLs (almost 85%) are of B-cell origin.** NHL is the **most common hematopoietic neoplasm** and is five times more common than HL.

History/PE

The median patient age is > **50 years,** but NHL may also be found in children, who tend to have more aggressive, higher-grade disease. Patient presentation varies with disease (see Table 2.7-8), but often includes painless peripheral adenopathy, "B" symptoms (fevers, night sweats, weight loss), and masses on exam.

A

APL has a good prognosis, because it is responsive to all-trans-retinoic acid (ATRA) therapy. This AML subtype is also associated with an ↑ incidence of DIC and a chromosomal translocation involving chromosomes 15 and 17.

TABLE 2.7-7. Non-Hodgkin vs Hodgkin Lymphoma

nhl	hl
Many peripheral nodes involved, extranodal, noncontiguous spread.	Single group of localized nodes, spreads contiguously and rarely involves extranodal sites.
Mainly B cells, sometimes T cells.	**Reed-Sternberg cells:** Distinct CD15+ and CD 30+ B cells.
Peak incidence 65–75 years old	Bimodal: young and old.
HIV and autoimmune association.	EBV association.

Adapted with permission from Le T et al. First Aid for the USMLE Step 1 2015. New York, NY: McGraw-Hill; 2015.

TABLE 2.7-8. Non-Hodgkin Lymphoma Types

B-CELL NEOPLASMS		
Follicular lymphoma	Adults (mean age 55)	▪ **Indolent course or low grade.** ▪ Painless waxing and waning adenopathy. ▪ Localized disease (15%) may be cured with radiation therapy.
Diffuse large B-cell lymphoma	Usually middle-aged and elderly	▪ **Intermediate grade.** ▪ **Most common NHL in adults.** ▪ Often presents with single rapidly growing mass. ▪ High cure rate with **R-CHOP therapy.**
Burkitt lymphoma	Children and adolescents	▪ **High grade,** "starry sky" appearance on lesion biopsy. ▪ Jaw lesion in Africa, abdominal lesion in Americas. ▪ Associated with **EBV** and t(8;14) translocation. ▪ Aggressive treatment with chemotherapy.
Mantle cell lymphoma	Elderly men	▪ CD5+. ▪ Rarest form of NHL.
T-CELL NEOPLASMS		
Adult T-cell lymphoma	Adults	▪ **High grade,** can progress to ALL. ▪ Presents with cutaneous lesions. ▪ Caused by **HTLV,** associated with IVDA.
Mycosis fungoides/Sézary syndrome	Adults	▪ Mycosis fungoides is a **T-cell lymphoma of the skin.** ▪ Cutaneous eczema-like lesions and pruritus are common presentations. ▪ **On skin biopsy see "cerebriform" lymphoid cells.** ▪ Can progress to Sézary syndrome (T-cell leukemia) with characteristic Sézary cells **seen on blood smear.**

Adapted with permission from Le T et al. First Aid for the USMLE Step 1 2015. New York, NY: McGraw-Hill; 2015.

KEY FACT

The treatment of high-grade NHL may be complicated by tumor lysis syndrome, in which rapid cell death releases intracellular contents and leads to hyperkalemia, hyperphosphatemia, hyperuricemia, and hypocalcemia.

KEY FACT

On physical exam, lymph nodes suspicious for malignancy are generally described as firm, fixed, nontender, circumscribed, rubbery, and > 1 cm in diameter. Benign nodes (usually from infection) are generally described as bilateral, < 1 cm, mobile, nontender (viral), or tender (bacterial).

KEY FACT

Chemotherapy and radiation can lead to 2° neoplasms such as AML, NHL, breast cancer, and thyroid cancer. Preventive measures such as mammography are warranted.

Diagnosis

- Best initial test: **Excisional lymph node biopsy.** Disease staged via Ann Arbor classification as follows. Stage I, single site involved; stage II, two sites involved on same side of the diaphragm; stage III, multiple sites involved on both sides of the diaphragm; stage IV, diffuse disease. "A" indicates no systemic symptoms; "B" indicates systemic symptoms.
- A CSF examination should be done in patients with HIV, neurologic symptoms, or 1° CNS lymphoma.

Treatment

- Treatment is based on histopathologic classification rather than on stage and consists of radiation, chemotherapy, or both.
- Generally, for low-grade indolent NHL, treatment is palliative.
- For high-grade aggressive NHL, treatment is aggressive with a curative approach.

Hodgkin Lymphoma

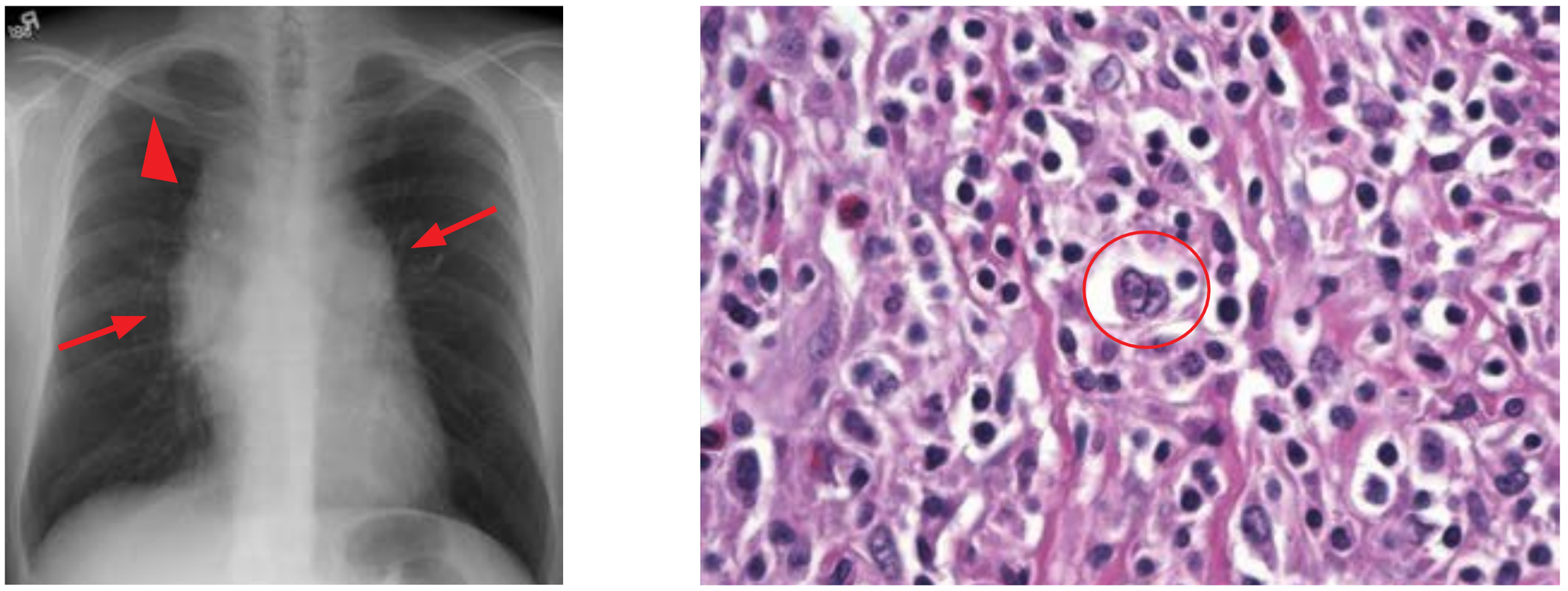
A **predominantly B-cell malignancy** associated with EBV. HL has a **bimodal age distribution:** age 30 (primarily the nodular sclerosing type) and age 60 (mainly the lymphocyte-depleted type). It has a male predominance in childhood.

History/PE

- HL commonly presents **above the diaphragm (classically as cervical adenopathy;** see Figure 2.7-17A). Infradiaphragmatic involvement suggests disseminated disease.
- Patients can have **systemic B symptoms** (see Table 2.7-7), **pruritus, and hepatosplenomegaly. Pel-Ebstein fevers** (1–2 weeks of high fever alternating with 1–2 afebrile weeks) and **alcohol-induced pain** at nodal sites are rare signs specific for HL.

Diagnosis

- Best initial step is an **excisional lymph node biopsy** showing the classic **Reed-Sternberg cells** (giant abnormal B cells with bilobar nuclei and



A B

FIGURE 2.7-17. Hodgkin lymphoma. (A) CXR of a 27-year-old man presenting with several weeks of fevers and night sweats shows bulky bilateral hilar (arrows) and right paratracheal (arrowhead) lymphadenopathy. **(B)** Lymph node sampling shows a mixed inflammatory infiltrate and a classic binucleate Reed-Sternberg cell (circle) consistent with Hodgkin lymphoma. (Reproduced with permission from USMLE-Rx.com.)

huge, eosinophilic nucleoli, which create an "owl's-eye" appearance; see Figure 2.7-17B).
- Staging is based on the **number of nodes, the presence of B symptoms, and whether the disease involves sites on both sides of the diaphragm.**

Treatment

- Treatment is stage dependent, involving chemotherapy and/or radiation.
- Five-year survival rates are 90% for stage I and II disease (nodal disease limited to one side of the diaphragm), 84% for stage III, and 65% for stage IV. **Lymphocyte-predominant HL has the best prognosis.**

Plasma Cell Disorders

MULTIPLE MYELOMA

Clonal proliferation of malignant plasma cells with **excessive production of monoclonal immunoglobulins** (typically **ineffective** IgA or **IgG**) or **immunoglobulin fragments** (kappa/lambda light chains). MM primarily affects the elderly, peaking in the seventh decade. Risk factors include radiation, monoclonal gammopathy of undetermined significance (MGUS), and, possibly, petroleum products and pesticides.

History/Pe

- Seventy percent of MM patients present with **bone pain** or with a pathologic fracture (MM cells infiltrate bone marrow, where they **activate osteoclasts,** creating **lytic lesions** and weak bones). **Anemia, hypercalcemia,** and **renal abnormalities** are also seen.
- Patients are prone to **infection** (IgG and IgA produced by myeloma cells are **monoclonal,** thus making them **ineffective**) and have **elevated monoclonal (M) proteins** in the serum and/or urine.

Diagnosis

- Best initial test: **Serum protein electrophoresis** showing **IgG** or **IgA** monoclonal spikes (see Figure 2.7-18).
- Most accurate test: Bone marrow biopsy **showing > 10% monoclonal** CD138+ plasma cells.
- CBC with smear may show **rouleaux** formation, whereas a urinalysis may show **Bence Jones protein** (paraprotein). **Total protein:albumin gap is often elevated.**
- M protein alone is insufficient for the diagnosis of MM, as MGUS, CLL, lymphoma, Waldenström macroglobulinemia, and amyloidosis can also ↑ M protein.
- Patients should also be evaluated with a skeletal survey (see Figure 2.7-19).

Treatment

- Young patients (< 70 years) can be treated with an **autologous bone marrow transplant.**
- Older patients are treated with **melphalan** (an oral alkylating agent) and prednisone.

KEY FACT

Chemotherapy often induces nausea in cancer patients and should be managed with **ondansetron** (Zofran), a serotonin 5-HT_3 receptor antagonist.

MNEMONIC

For MM think CRAB—

hyper**C**alcemia
Renal involvement
Anemia
Bone lytic lesions/**B**ack pain

KEY FACT

MGUS is also a monoclonal expansion of plasma cells that is **asymptomatic** and may eventually lead to multiple myeloma (1–2% per year). No "CRAB" findings.

KEY FACT

Hypercalcemia symptoms: renal stones, bone and abdominal pain, confusion, polyuria, weakness and nausea.

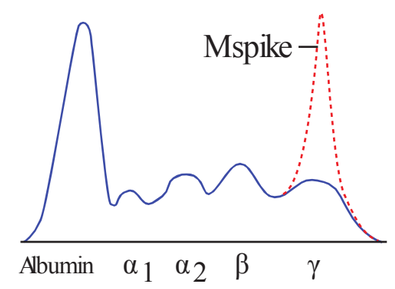


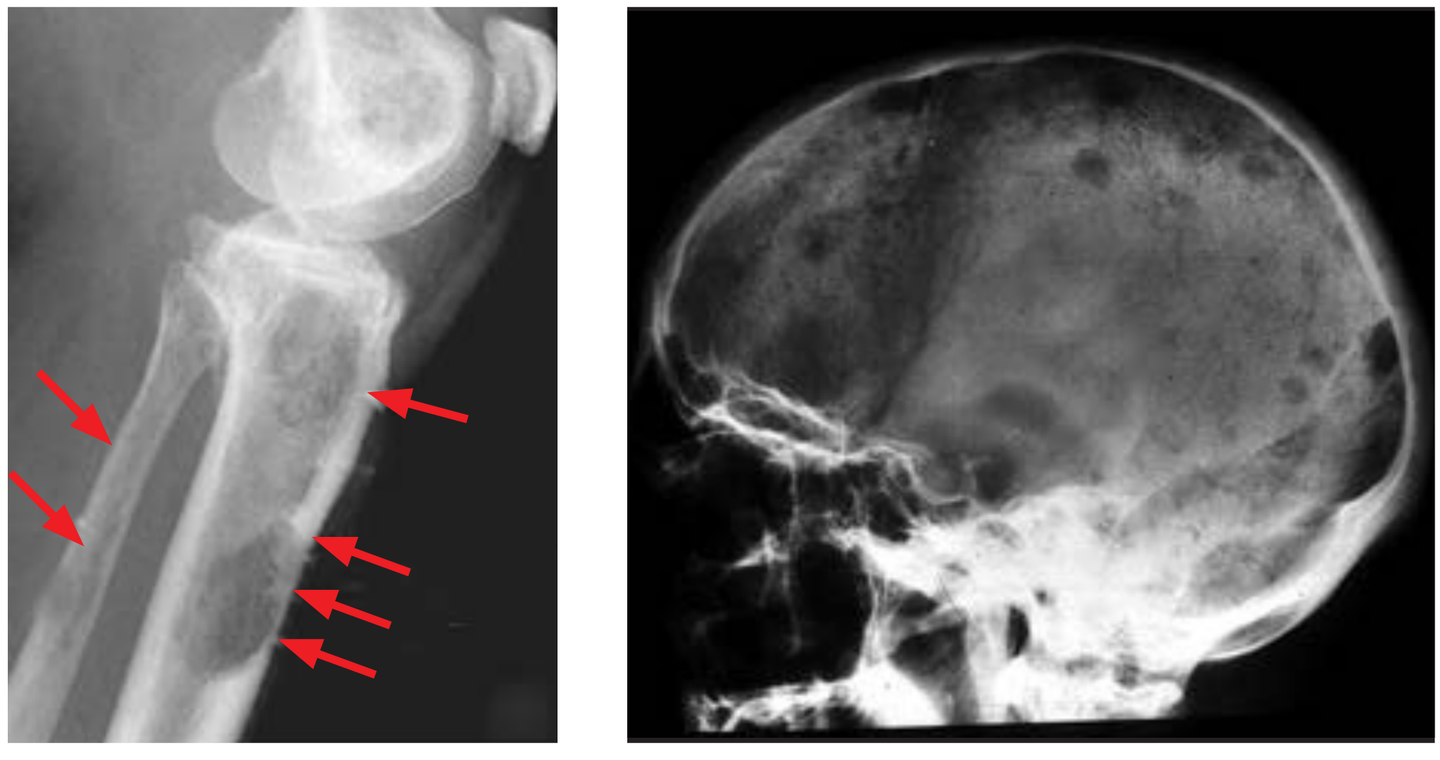
FIGURE 2.7-18. Multiple myeloma. Serum protein electrophoretic tracing showing M protein spike IgG/A (diagnostic of MM). Note that M protein spike IgM indicates Waldenström macroglobulinemia. (Reproduced with permission from Le T et al. First Aid for the USMLE Step 1 2015. New York, NY: McGraw-Hill; 2015.)

KEY FACT

MM damaging renal tubules can produce an **adult Fanconi syndrome.**

KEY FACT

Because MM is an osteoclastic process, a bone scan, which detects osteoblastic activity, may be ⊖.



A B

FIGURE 2.7-19. Multiple myeloma skeletal survey. Characteristic lytic bony lesions of multiple myeloma involving the tibia and fibula **(A)** and the skull **(B)** are seen. (Part A reproduced with permission from Lichtman MA et al. Williams Hematology, 8th ed. New York, NY: McGraw-Hill; 2010. Part B reproduced with permission from Kantarjian HM, Wolff RA, Koller CA. MD Anderson Manual of Medical Oncology, 2nd ed. New York, NY: McGraw-Hill; 2011.)

WALDENSTRÖM MACROGLOBULINEMIA

A clonal disorder of B cells that leads to a malignant monoclonal gammopathy. ↑ **levels of IgM** result in **hyperviscosity syndrome,** coagulation abnormalities, cryoglobulinemia, cold agglutinin disease (leading to autoimmune hemolytic anemia), and amyloidosis. Tissue is infiltrated by IgM and neoplastic plasma cells. A **chronic, indolent disease of the elderly.**

KEY FACT

Cryoglobulinemia and cold agglutinins are different disorders caused by IgM antibodies. Cryoglobulinemia is most often seen in HCV and has systemic signs such as joint pain and renal involvement. Cold agglutinins cause numbness upon cold exposure and are seen with EBV, mycoplasmal infection, and Waldenström macroglobulinemia.

History/Pe

- Presents with nonspecific symptoms: lethargy, weight loss, and **Raynaud phenomenon** from cryoglobulinemia. **Neurologic problems** ranging from mental status changes to sensorimotor peripheral neuropathy and blurry vision (**engorged blood vessels** can be noted on eye exam) are also seen. Organomegaly and organ dysfunction can be present.
- As with multiple myeloma, **MGUS is a precursor** to disease.

Diagnosis

- Most accurate test: **Bone marrow biopsy and aspirate.** Marrow shows abnormal plasma cells, classically with **Dutcher bodies** (PAS-⊕ IgM deposits around the nucleus). Serum and urine protein electrophoresis and immunofixation are also used.
- Nonspecific labs show ↑ ESR, uric acid, LDH, and alkaline phosphatase.

Treatment

Chemo for underlying malignancy. Plasmapheresis to remove excess immunoglobulin.

AMYLOIDOSIS

Extracellular **deposition of amyloid protein fibrils** due to a variety of causes (see Table 2.7-9). Classically a disease of the **elderly.**

TABLE 2.7-9. Types of Amyloidosis

Amyloid	Cause
AL	A plasma cell dyscrasia with deposition of monoclonal light-chain fragments. Associated with multiple myeloma and Waldenström macroglobulinemia.
AA	Deposition of the acute-phase reactant serum amyloid A. Associated with chronic inflammatory diseases (eg, rheumatoid arthritis), infections, and neoplasms.
Dialysis related	Deposition of β_2-microglobulin, which accumulates in patients on long-term dialysis.
Heritable	Deposition of abnormal gene products (eg, transthyretin, aka prealbumin). A heterogeneous group of disorders.
Senile-systemic	Deposition of otherwise normal transthyretin.

AA = 2° amyloidosis; AL = 1° amyloidosis.

History/Pe

- Clinical presentation depends on the type, amount, and tissue distribution of amyloid. In the most common forms of systemic amyloidosis, 1° (AL) and 2° (AA), the major sites of clinically important amyloid deposition are in the **kidneys, heart, and liver.**
- In some disorders, amyloid deposition is limited to one organ (the brain in **Alzheimer disease**).

Diagnosis

Most accurate test: Tissue biopsy with **Congo red staining** showing apple-green birefringence under polarized light. Immunohistochemistry can identify the amyloid protein type.

Treatment

1° amyloidosis is treated with experimental chemotherapy and autologous stem cell transplant; in 2° amyloidosis, the underlying condition should be addressed.

Neutropenia

An absolute neutrophil count (ANC) < 1500/mm³, where ANC = (WBC count) × (% bands + % segmented neutrophils). Neutropenia may be due to a combination of ↓ production, migration away from the vascular space, and ↑ destruction or utilization. It may be acquired or intrinsic. **The most common causes of neutropenia in adults are infections followed by drugs.** Other common causes include diseases that infiltrate the bone marrow such as leukemias or lymphomas, aplastic anemias, or B_{12}/folate deficiencies.

History/Pe

- Patients are at ↑ **risk of infection.** The lower the neutrophil count, the higher the risk.

Q 1

A 71-year-old man seeks care for marked lethargy and constipation that are worsening. He also notes a dull back pain that is present at most times, even at night. His lab studies have been normal with the exception of an ↑ creatinine level. What is most likely responsible for the patient's worsening renal function?

Q 2

An 80-year-old man is seen in your clinic after an incidental finding of elevated IgG on a recent hospital admission for pneumonia. He has no signs of kidney damage, anemia, or bone lesions. The IgG level is 2100 mg/dL, and a subsequent bone marrow biopsy shows 3% plasma cells. What is the next best step?

- **Acute neutropenia:** Associated with S aureus, Pseudomonas, E coli, Proteus, and Klebsiella **sepsis.**
- **Chronic and autoimmune neutropenia:** Presents with **recurrent sinusitis, stomatitis, gingivitis,** and **perirectal infections** rather than sepsis. Some chronic neutropenias are accompanied by splenomegaly (Felty syndrome, Gaucher disease, sarcoidosis).

Diagnosis

- Best initial test is a CBC with smear.
- In the history, look for drug or toxin exposure, infection, autoimmune, or neoplastic disease.
- Follow neutropenia clinically with a CBC and ANC. If thrombocytopenia or anemia is present, bone marrow biopsy and aspirate should be performed.
- **Serum immunologic evaluation, ANA levels, and a workup for collagen vascular disease may be merited.**

KEY FACT

Hypothermia can be caused by fungemia.

Treatment

- **Infection management:** Neutropenic patients can't mount an effective inflammatory response.
- Fever in the context of neutropenia (neutropenic fever) is a **medical emergency** and should be treated immediately with **broad-spectrum antibiotics such as cefepime.** Suspected fungal infections should be treated appropriately as well.
- Hematopoietic stem cell factors such as **G-CSF** can be used to shorten the duration of neutropenia. Rarely, **IVIG and allogeneic bone marrow transplantation** may be used.

MNEMONIC

Causes of 2° eosinophilia—

NAACP

Neoplasm
Allergies
Asthma
Collagen vascular disease
Parasites

Eosinophilia

An **absolute eosinophil count > 350/mm.** Eosinophilia can be triggered by the overproduction of cytokines (IL-3, IL-5, and GM-CSF) or by chemokines that stimulate the migration of eosinophils into peripheral blood and tissues. Eosinophilia may be a 1° disorder but is usually 2° to another cause. The most common cause in the developed world is **allergy,** whereas in the developing world it is **parasitic infection.**

History/Pe

- A **travel, medication, atopic, lymphoma/leukemia,** and **diet history** should be elicited.
- Exam varies by cause. Patients with hypereosinophilic syndrome (HES) may present with fever, anemia, and prominent cardiac findings (emboli from mural thrombi, abnormal ECGs, CHF, murmurs). Eosinophils can infiltrate and affect other organs as well.

Diagnosis

- CBC with differential should be obtained. **CSF analysis showing eosinophilia** is suggestive of a drug reaction or infection with coccidioidomycosis or a helminth.
- **Hematuria with eosinophilia can be a sign of schistosomiasis.**

1 A

Patients with multiple myeloma frequently have renal dysfunction 2° to urinary immunoglobulins, also known as Bence Jones protein, that have the ability to form casts, leading to cast nephropathy.

2 A

This patient has MGUS, as seen by the elevated IgG in the absence of other clinical abnormalities or symptoms. No treatment is required, but because MGUS can progress to MM, this patient should be seen regularly for signs of renal failure, anemia, or bone pain.

Treatment

New-onset cardiac findings, eosinophilia > 100,000/mm^3 or drug reactions with systemic symptoms and eosinophilia must be spotted early and should be treated with **steroids** (and discontinuation of offending agents).

Transplant Medicine

- Three types of tissue transplantation are increasingly used to treat diseases:
  - **Autologous:** Transplantation from the patient to him/herself.
  - **Allogeneic:** Transplantation from a donor to a genetically different patient.
  - **Syngeneic:** Transplantation between identical twins (from a donor to a genetically identical patient).
- With allogeneic donation, efforts are made to ABO and HLA match the donor and recipient. Despite matching and immunosuppression, however, transplants may be rejected. There are three types of solid organ rejection: hyperacute, acute, and chronic (see Table 2.7-10).
- Graft-vs-host disease (GVHD) is a complication specific to allogeneic bone marrow transplantation in which donated T cells attack host tissues, especially the skin, liver, and GI tract. It may be acute (< 100 days post-transplant) or chronic (> 100 days afterward).
  - **Minor histocompatibility antigens are thought to be responsible for GVHD,** which presents with **skin changes, cholestatic liver dysfunction, obstructive lung disease,** or **GI problems.**
  - Patients are treated with high-dose corticosteroids.
- Typical posttransplant immunosuppression regimens include: prednisone, mycophenolate mofetil (MMF), FK506 (tacrolimus) to suppress immune-mediated rejection, TMP-SMX, ganciclovir, and ketoconazole to prevent subsequent infection in the immunosuppressed host.
- A variant of GVHD is the **graft-vs-leukemia effect,** in which leukemia patients who are treated with an allogeneic bone marrow transplant have

TABLE 2.7-10. Types of Solid Organ Transplant Rejection

Variable	hyperacute	acute	chronic
Timing after transplant	Within minutes.	Between 5 days and 3 months.	Months to years.
Pathomechanism	Preformed antibodies.	T-cell mediated.	Chronic immune reaction causing fibrosis.
Tissue finding	Vascular thrombi; tissue ischemia.	Laboratory evidence of tissue destruction such as ↑ GGT, alkaline phosphatase, LDH, BUN, or creatinine.	Gradual loss of organ function.
Prevention	Check ABO compatibility.	N/A	N/A
Treatment	Cytotoxic agents.	Confirm with sampling of transplanted tissue; treat with corticosteroids, antilymphocyte antibodies (OKT3), tacrolimus, or MMF.	No treatment; biopsy to rule out treatable acute reaction.

significantly lower relapse rates than those treated with an autologous transplant. This difference is thought to be due to a reaction of donated T cells against leukemic cells.

Diseases Associated With Neoplasms

Table 2.7-11 outlines conditions that are commonly associated with neoplasms.

TABLE 2.7-11. Disorders Associated With Neoplasms

Condition	Neoplasm
Xeroderma pigmentosum	Squamous cell and basal cell carcinomas of the skin.
Actinic keratosis	Squamous cell carcinoma of the skin.
Multiple dysplastic nevi	Malignant melanoma.
Down syndrome	ALL ("We will **ALL** go **Down** together").
Immunodeficiency states	Malignant lymphomas.
AIDS	Aggressive malignant NHLs and Kaposi sarcoma.
Autoimmune diseases (eg, myasthenia gravis)	Benign and malignant thymomas.
Chronic atrophic gastritis, pernicious anemia, postsurgical gastric remnants	Gastric adenocarcinoma.
Barrett esophagus (chronic GI reflux	Esophageal adenocarcinoma.
Plummer-Vinson syndrome (atrophic glossitis, esophageal webs, anemia; all due to iron deficiency)	Squamous cell carcinoma of the esophagus.
Ulcerative colitis	Colonic adenocarcinoma.
Cirrhosis (alcoholic, HBV, HCV, Wilson disease, etc)	Hepatocellular carcinoma.
Acanthosis nigricans (hyperpigmentation and epidermal thickening)	Visceral malignancy (stomach, lung, breast, uterus).
Tuberous sclerosis (facial angiofibroma, seizures, mental retardation)	Astrocytoma and cardiac rhabdomyoma.
Paget disease of bone	2° osteosarcoma and fibrosarcoma.

HIGH-YIELD FACTS IN

INFECTIOUS DISEASE

Respiratory Infections 196
- Pneumonia 196
- Tuberculosis 199
- Acute Pharyngitis 200
- Sinusitis 201
- Coccidioidomycosis 202
- Influenza 203

CNS Infections 204
- Meningitis 204
- Encephalitis 206
- Brain Abscess 207

Human Immunodeficiency Virus 208

Opportunistic Infections 210
- Oropharyngeal Candidiasis (Thrush) 211
- Cryptococcal Meningitis 211
- Histoplasmosis 211
- Pneumocystis jirovecii Pneumonia 212
- Cytomegalovirus 213
- mycobacterium avium complex 214
- Toxoplasmosis 214

Sexually Transmitted Diseases 215
- Chlamydia 215
- Gonorrhea 216
- Syphilis 217
- Genital Lesions 219

Genitourinary Infections 219
- Urinary Tract Infections 219
- Pyelonephritis 221

Hematologic Infections 221
- Sepsis 221
- Malaria 222
- Infectious Mononucleosis 223

Fever 225
- Fever of Unknown origin 225
- Neutropenic Fever 225

Tick-Borne Infections 226
- Lyme disease 226
- Rocky Mountain Spotted Fever 227

Infections of the Eyes and Ears 228
- Infectious conjunctivitis 228
- orbital cellulitis 228
- otitis Externa 229

Miscellaneous Infections 230
- Infective Endocarditis 230
- Anthrax 232
- osteomyelitis 233

Respiratory Infections

PNEUMONIA

Some common causes of pneumonia are outlined in Tables 2.8-1 and 2.8-2.

History/Pe

- **May present classically or atypically.**
  - **Classic symptoms:** Sudden onset, **fever, productive cough** (purulent yellow-green sputum or hemoptysis), dyspnea, night sweats, **pleuritic chest pain.**
  - **Atypical symptoms:** Gradual onset, dry cough, headaches, myalgias, sore throat, GI symptoms.
- Lung examination may show ↓ or bronchial breath sounds, rales, wheezing, dullness to percussion, egophony, and/or tactile fremitus.
- Elderly patients and those with COPD, diabetes, or immune compromise may have minimal or atypical signs on physical examination.

KEY FACT

An adequate sputum Gram stain sample has many PMNs (> 25 cells/hpf) and few epithelial cells (< 10 cells/hpf).

Diagnosis

- Diagnosis requires two or more symptoms of acute respiratory infection plus a new infiltrate on CXR or CT.
- Workup includes physical examination, **CXR** (see Figure 2.8-1), CBC. Most cases are treated empirically in the outpatient setting. Sputum Gram stain and culture (see Figure 2.8-2), nasopharyngeal aspirate, blood culture, and ABG are obtained in minority of cases, mostly in hospitalized patients or outpatients with persistent symptoms.
- Tests for specific pathogens include the following:
  - Legionella: Urine Legionella antigen test, sputum staining with direct fluorescent antibody (DFA), culture.
  - Chlamydophila (Chlamydia): Serologic testing, PCR (polymerase chain reaction).
  - Mycoplasma: Usually clinical. Serum cold agglutinins and serum Mycoplasma antigen may also be used.
  - S pneumoniae: Urine pneumococcal antigen test, culture.
  - **Viral:** Nasopharyngeal aspirate, rapid molecular tests for pathogens (eg, influenza, respiratory syncytial virus), DFA, viral culture.

KEY FACT

CURB-65. Pneumonia hospitalization criteria, 2–3 = consider inpatient treatment; > 4 = admission.

- **C**onfusion
- **U**remia (BUN > 19)
- **R**espiratory rate (> 30 breaths/min)
- **B**lood pressure (SBP < 90 mm Hg or DBP < 60 mm Hg)
- Age > **65** years

TABLE 2.8-1. Common Causes of Pneumonia by Age

Neonates	Children (6 Weeks–18 years)	Adults (18–40 years)	Adults (40–65 years)	Elderly
Group B streptococci (GBS)	Viruses	Mycoplasma	S pneumoniae	S pneumoniae
Escherichia coli	Streptococcus pneumoniae	S pneumoniae	Haemophilus influenza	H influenza
Listeria	Mycoplasma	Viruses	Mycoplasma	Viruses
	Chlamydia pneumoniae	C pneumoniae	Viruses	Staphylococcus aureus
	S aureus		Anaerobes	Gram-⊖ rods (GNRs)
				Anaerobes

TABLE 2.8-2. Causes of Pneumonia by Category

Category	Etiology
Atypical	Mycoplasma, Legionella, Chlamydophila (Chlamydia).
Nosocomial (hospital acquired)	GNRs, Staphylococcus, anaerobes, Pseudomonas (intubated patients).
Immunocompromised	Staphylococcus, gram-⊕ rods, fungi, viruses, Pneumocystis jirovecii (with HIV), mycobacteria.
Aspiration	Anaerobes.
Alcoholics/IV drug users	S pneumoniae, Klebsiella, Staphylococcus.
Cystic fibrosis (CF)	Staphylococcus, Pseudomonas, Burkholderia, mycobacteria.
COPD	H influenza, Moraxella catarrhalis, S pneumoniae.
Postviral	Staphylococcus, S pneumoniae, H influenza.
Neonates	GBS, E coli, Listeria.
Recurrent	Obstruction, bronchogenic carcinoma, lymphoma, Wegener granulomatosis, immunodeficiency, unusual organisms (eg, Nocardia, Coxiella burnetii, Aspergillus, Pseudomonas).

Treatment

Table 2.8-3 summarizes the recommended initial treatment for pneumonia.

- Outpatient treatment with oral antibiotics is recommended in uncomplicated cases.

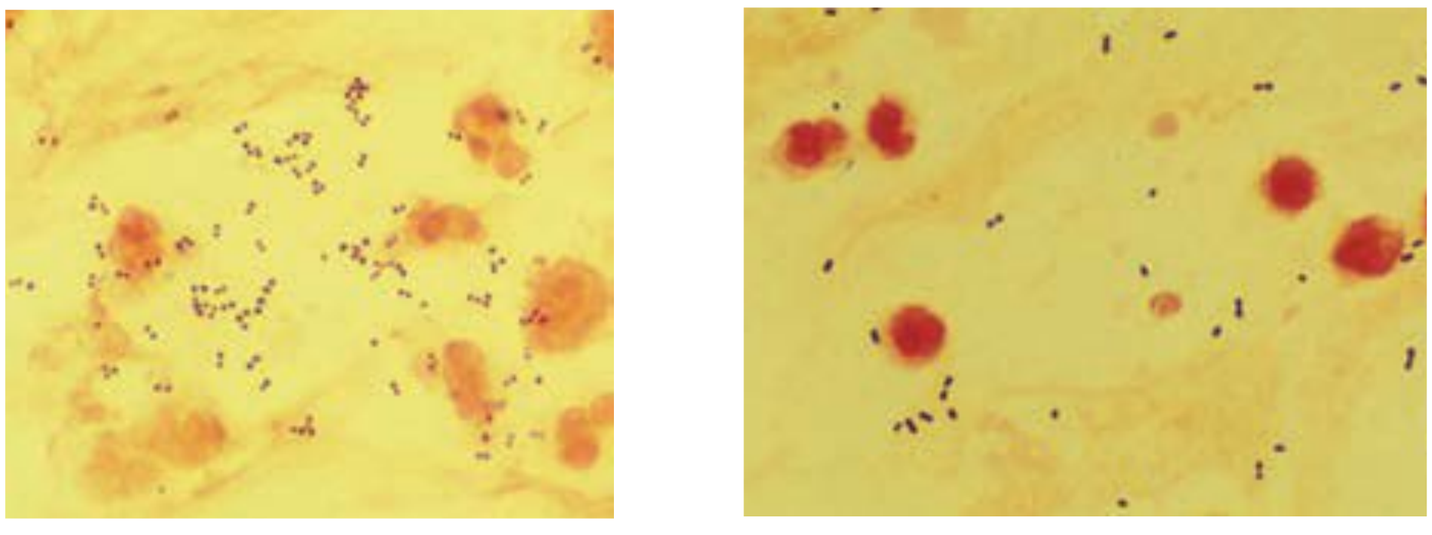


A B

FIGURE 2.8-1. Lobar pneumonia. PA **(A)** and lateral **(B)** CXRs of a 41-year-old man with cough and shortness of breath show a left lower lobe opacity consistent with lobar pneumonia. S pneumoniae was confirmed by sputum Gram stain and culture. (Reproduced with permission from USMLE-Rx.com.)

KEY FACT

The pneumococcal vaccine should be given to all children, patients > 65 years old, people with splenic dysfunction (eg, sickle cell) or without a spleen, immunocompromised patients, and patients with chronic disease.



A B

FIGURE 2.8-2. Common pathogens causing pneumonia. (A) S aureus. These clusters of gram-⊕ cocci were isolated from the sputum of a patient who developed pneumonia while hospitalized. **(B)** S pneumoniae. Sputum sample from a patient with pneumonia. Note the characteristic lancet-shaped gram-⊕ diplococci.

- For patients with obstructive diseases (eg, CF or bronchiectasis), consider adding pseudomonal, staphylococcal, or anaerobic coverage.

Complications

Pleural effusion, empyema, lung abscess, necrotizing pneumonia, bacteremia.

TABLE 2.8-3. Treatment of Pneumonia

Patient type	Suspected pathogens	Empiric coverage
Outpatient community-acquired pneumonia, ≤ 65 years, otherwise healthy, no antimicrobials within 3 months.	S pneumoniae, Mycoplasma pneumoniae, C pneumoniae, H influenza, viral.	Macrolide or doxycycline.
> 65 years or comorbidity (COPD, heart failure, renal failure, diabetes, liver disease, EtOH abuse) or antimicrobial use within 3 months.	S pneumoniae, H influenza, aerobic GNRs (E coli, Enterobacter, Klebsiella), S aureus, Legionella, viruses.	Fluoroquinolone or β-lactam + macrolide.
Community-acquired pneumonia requiring hospitalization.	S pneumoniae, H influenza, anaerobes, aerobic GNRs, Legionella, Chlamydia.	Fluoroquinolone or antipneumococcal β-lactam + macrolide.
Community-acquired pneumonia requiring ICU care.	S pneumoniae, Legionella, H influenza, anaerobes, aerobic GNRs, Mycoplasma, Pseudomonas.	Antipneumococcal β-lactam + either azithromycin or fluoroquinolone.
Institution-/hospital-acquired pneumonia—hospitalized > 48 hours or in a long-term care facility > 14 days; ventilator-associated pneumonia.	GNRs (including Pseudomonas and Acinetobacter), S aureus, Legionella, mixed flora.	Extended-spectrum cephalosporin or carbapenem with antipseudomonal activity. Add an aminoglycoside or a fluoroquinolone for coverage of resistant organisms (Pseudomonas) until lab sensitivities identify the best single agent.
Critically ill or worsening over 24–48 hours on initial antibiotic therapy.	MRSA.	Add vancomycin or linezolid; broader gram-⊖ coverage.

TUBERCULOSIS

Infection due to Mycobacterium tuberculosis. Roughly 2 billion people worldwide are infected with TB. Initial infection usually leads to latent TB infection that is asymptomatic. Most symptomatic cases (ie, active disease) are due to reactivation of latent infection rather than to 1° exposure. Pulmonary TB is most common, but disseminated or extrapulmonary TB can occur as well. TB can infect almost any organ system, including the lungs, CNS, GU tract, bone, and GI tract. Risk factors include the following:

- **Risk factors for active disease** (ie, reactivation): Immunosuppression (HIV/AIDS), alcoholism, preexisting lung disease, diabetes, advancing age.
- **Risk factors for TB exposure in the United States: Homelessness** and crowded living conditions (eg, **prisons**), emigration/travel from developing nations, employment in a health profession, interaction with known TB contacts.

History/Pe

- Presents with cough, **hemoptysis,** dyspnea, **weight loss, fatigue, night sweats, fever,** cachexia, hypoxia, tachycardia, lymphadenopathy, an abnormal lung examination, and prolonged (> 3 weeks) symptom duration.
- TB is a common cause of fever of unknown origin (FUO).
- HIV patients can present with atypical signs and symptoms and have higher rates of extrapulmonary TB.

Diagnosis

- **Active disease:** Mycobacterial culture of sputum (or blood/tissue for extrapulmonary disease) is the gold standard but can take weeks to obtain. A sputum **acid-fast stain** (see Figure 2.8-3) can yield rapid preliminary results but lacks sensitivity.
  - The most common finding among typical hosts is a cavitary infiltrate in the upper lobe on CXR (see Figure 2.8-4), which may be accompanied calcification of one or more nearby lymph nodes **(Ghon complex).**

KEY FACT

TB almost always presents with an extended duration (> 3 weeks) of symptoms.

KEY FACT

The interpretation and management of the PPD skin test is the same for patients who have received the BCG vaccine and those who have not.

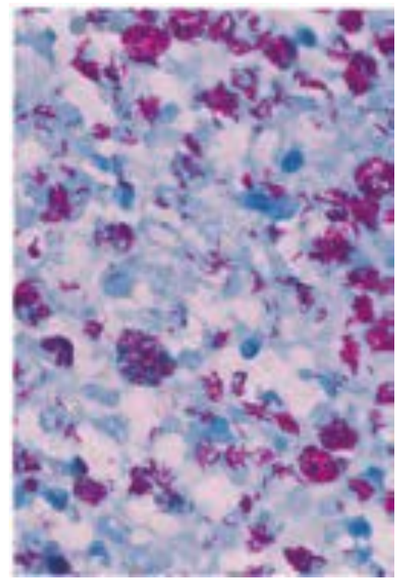
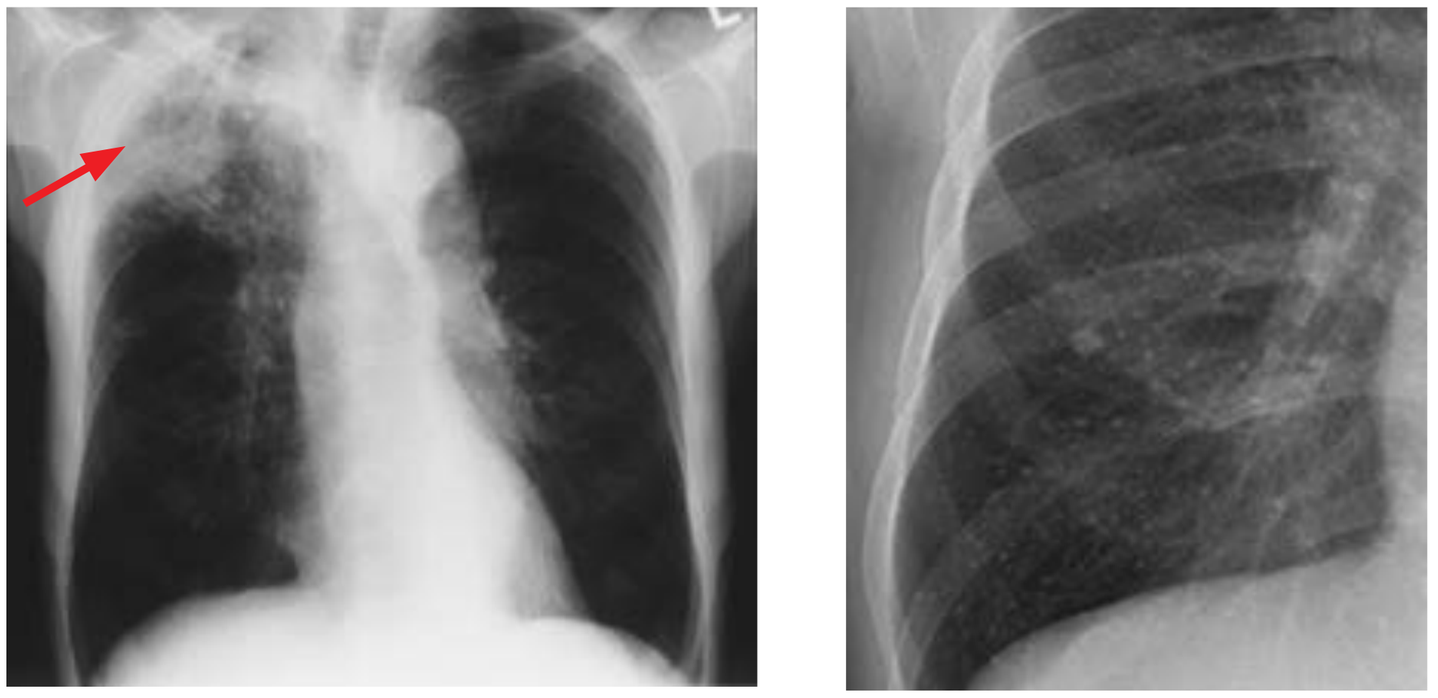


FIGURE 2.8-3. Tuberculosis. Note the red color ("red snappers") of tubercle bacilli on acid-fast staining. (Reproduced with permission from Milikowski C. Color Atlas of Basic Histopathology, 1st ed. Stamford, CT: Appleton & Lange; 1997.)



A B

FIGURE 2.8-4. Pulmonary TB. (A) Right apical opacity with areas of cavitation (arrow) is seen in an elderly man with reactivation TB. **(B)** Coned-in view of a CXR in a young man with miliary TB shows innumerable 1- to 2-mm pulmonary nodules. (Part A reproduced with permission from Halter JB et al. Hazzard's Geriatric Medicine and Gerontology, 6th ed. New York, NY: McGraw-Hill; 2009. Part B reproduced with permission from USMLE-Rx.com.)

KEY FACT

Rifampin turns body fluids orange (including tears); ethambutol can cause optic neuritis. INH causes peripheral neuropathy and hepatitis.

- HIV patients or those with 1° TB may show lower lobe infiltrates with or without cavitation.
- Multiple fine nodular densities distributed throughout both lungs are typical of miliary TB, which represents hematologic or lymphatic dissemination.

- **Latent disease (asymptomatic and previous exposure):** Diagnose with a ⊕ PPD (see Figure 2.8-5) or QuantiFERON-TB test.
  - Immunocompromised individuals with latent TB infection may have a ⊖ PPD (anergy).
  - All patients with a ⊕ PPD should be evaluated with a CXR to rule out active disease.

Treatment

All cases (both latent and active) must be reported to local and state health departments. Respiratory isolation should be instituted if active TB is suspected. Treatment measures are as follows:

- **Active disease:**
  - Directly observed multidrug therapy with a four-drug regimen **(INH, pyrazinamide, rifampin, ethambutol)** × 2 months followed by INH and rifampin × 4 months.
  - Administer **vitamin B_6** (pyridoxine) with **INH** to prevent peripheral neuropathy.
- **Latent disease:** For a ⊕ PPD without signs or symptoms of active disease, treat with **INH × 9 months.** Alternative regimens include INH × 6 months or rifampin × 4 months.

MNEMONIC

Patients with TB are RIPE for treatment—

Rifampin
INH
Pyrazinamide
Ethambutol

ACUTE PHARYNGITIS

KEY FACT

Early antibiotic treatment of streptococcal pharyngitis can prevent rheumatic fever but not glomerulonephritis.

Viral causes are more common (90% in adults), but it is important to identify streptococcal pharyngitis **(group A β-hemolytic** Streptococcus pyogenes**).** Etiologies are as follows:

- **Bacterial:** Group A streptococci (GAS), Neisseria gonorrhoeae, Corynebacterium diphtheriae, M pneumoniae.
- **Viral:** Rhinovirus, coronavirus, adenovirus, HSV, EBV, CMV, influenza virus, coxsackievirus, acute HIV infection.

PPD is injected intradermally on the volar surface of the forearm. The diameter of induration is measured at 48–72 hours. BCG vaccination typically renders a patient PPD ⊕ but should not preclude prophylaxis as recommended for unvaccinated individuals. The size of induration that indicates a ⊕ test is interpreted as follows:

- ≥ 5 mm: HIV or risk factors, close TB contacts, CXR evidence of TB.
- ≥ 10 mm: Indigent/homeless, residents of developing nations, IV drug use, chronic illness, residents of health and correctional institutions, and health care workers.
- ≥ 15 mm: Everyone else, including those with no known risk factors.

A ⊖ reaction with ⊖ controls implies anergy from immunosuppression, old age, or malnutrition and thus does not rule out TB.

FIGURE 2.8-5. PPD interpretation.

History/Pe

- **Typical of streptococcal pharyngitis: Fever, sore throat, pharyngeal erythema** (see Figure 2.8-6), **tonsillar exudate,** cervical lymphadenopathy, soft palate petechiae, headache, vomiting, scarlatiniform rash (indicates scarlet fever).
- **Atypical of streptococcal pharyngitis:** Coryza, hoarseness, rhinorrhea, **cough,** conjunctivitis, anterior stomatitis, ulcerative lesions, GI symptoms.



FIGURE 2.8-6. Pharyngeal erythema. Streptococcus pyogenes is the most common bacterial cause of pharyngitis. (Reproduced courtesy of the Centers for Disease Control and Prevention, Atlanta, GA.)

Diagnosis

Diagnosed by clinical evaluation, **rapid GAS antigen detection,** and **throat culture.** If three out of four Centor criteria are met (see Table 2.8-4), the sensitivity of rapid antigen testing is > 90%.

Treatment

If GAS is suspected, begin empiric antibiotic therapy with **penicillin** × 10 days. Cephalosporins, amoxicillin, and azithromycin are alternative options. Symptom relief can be attained with fluids, rest, antipyretics, and saltwater gargles.

Complications

- **Nonsuppurative:** Acute rheumatic fever (see the Cardiovascular chapter), poststreptococcal glomerulonephritis.
- **Suppurative:** Cervical lymphadenitis, mastoiditis, sinusitis, otitis media, retropharyngeal or peritonsillar abscess, and, rarely, thrombophlebitis of the jugular vein **(Lemierre syndrome)** due to Fusobacterium, an oral anaerobe.
- **Peritonsillar abscess** may present with odynophagia, trismus ("lockjaw"), a muffled "hot potato" voice, unilateral tonsillar enlargement, and erythema, with the uvula and soft palate deviated away from the affected side. Culture abscess fluid and localize the abscess via intraoral ultrasound or CT. Treat with antibiotics and **surgical drainage.**

SINUSITIS

Refers to inflammation of the paranasal sinuses. The maxillary sinuses are most commonly affected. Subtypes include the following:

TABLE 2.8-4. Modified Centor Criteria (Centor Criteria + Age)

Criteria	Points
Fever	1
Tonsillar exudate	1
Tender anterior cervical lymphadenopathy	1
Lack of cough	1
3–14 years of age	1
15–45 years of age	0
> 45 years of age	–1

If 4–5 points, treat empirically with antibiotics.

If 2–3 points, perform rapid antigen test. If ⊕ antigen test, treat with antibiotics; if ⊖ antigen test, perform throat culture.

If 0–1 points, no testing or antibiotics required, symptomatic treatment only.

Q

A 70-year-old man presents to the ED with 5 days of fever, productive cough, and altered mental status. He is also found to be hypotensive and tachypneic. Broad-spectrum antibiotics and fluid resuscitation are promptly administered, but the patient continues to be hypotensive. What is the next best step in treatment?

KEY FACT

Potential complications of sinusitis include meningitis, frontal bone osteomyelitis, cavernous sinus thrombosis, and abscess formation.

KEY FACT

Beware of invasive and life-threatening fungal sinusitis (caused by Mucor and Rhizopus) in patients with poorly controlled diabetes mellitus or immune compromise.

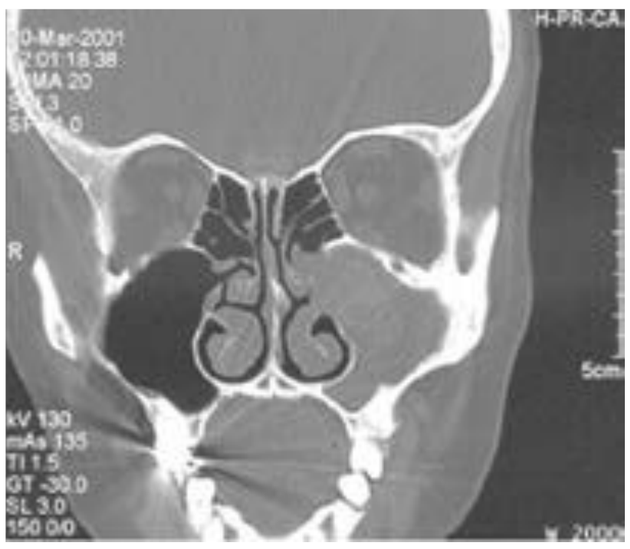


FIGURE 2.8-7. Sinusitis. Coronal CT image shows an opacified left maxillary sinus and marked associated bony thickening, consistent with chronic maxillary sinusitis. (Reproduced with permission from Lalwani AK. Current Diagnosis & Treatment in Otolaryngology—Head and Neck Surgery, 2nd ed. New York, NY: McGraw-Hill; 2008.)

- **Acute sinusitis (symptoms lasting < 1 month):** Most commonly associated with viruses, S pneumoniae, H influenzae, and M catarrhalis. Bacterial causes are rare and characterized by purulent nasal discharge, facial or tooth tenderness, hyposmia/anosmia, and symptoms lasting > 10 days.
- **Chronic sinusitis (symptoms persisting > 3 months):** A chronic inflammatory process often due to obstruction of sinus drainage and ongoing low-grade anaerobic infections.

History/Pe

- Presents with **fever, facial pain/pressure, headache,** nasal congestion, and discharge. Examination may reveal tenderness, erythema, and swelling over the affected area.
- High fever, leukocytosis, and a purulent nasal discharge are suggestive of acute bacterial sinusitis.

Diagnosis

- A clinical diagnosis. Culture and radiography are generally not required for acute sinusitis but may guide the management of chronic cases.
- Transillumination shows opacification of the sinuses (low sensitivity).
- CT is the test of choice for sinus imaging (see Figure 2.8-7) but is usually necessary only if symptoms persist after treatment.

Treatment

- Most cases of acute sinusitis are viral and/or self-limited and are treated with symptomatic therapy (decongestants, antihistamines, nasal saline lavage, pain relief).
- **Acute bacterial sinusitis:** Consider amoxicillin/clavulanate for 10 days or clarithromycin, azithromycin, trimethoprim-sulfamethoxazole (TMP-SMX), a fluoroquinolone, or a second-generation cephalosporin for 10 days.
- **Chronic sinusitis:**
  - Antibiotics are similar to those used for acute disease, although a **longer course** (3–6 weeks) may be necessary.
  - **Adjuvant** therapy with intranasal corticosteroids, decongestants, and antihistamines may be useful in combating the allergic/inflammatory component of the disease. **Surgical** intervention may be required.

COCCIDIOIDOMYCOSIS

A pulmonary fungal infection endemic to the **southwestern United States** (see Figure 2.8-8). Can present as an acute or subacute pneumonia or as a flulike illness, and may involve extrapulmonary sites, including bone, CNS, and skin (manifestations include erythema multiforme or erythema nodosum). The incubation period is 1–4 weeks after exposure. Filipino, black, pregnant, and HIV-⊕ patients are at ↑ risk for disseminated disease.

A

Administration of vasopressors and ICU admission. This patient is in septic shock, probably 2° to pneumonia. Patients with pneumonia who require vasopressors or mechanical ventilation warrant admission to an ICU.

History/Pe

Patients present with **fever,** anorexia, headache, chest pain, **cough,** dyspnea, arthralgias, and **night sweats.** Disseminated infection can present with meningitis, bone lesions, and soft tissue abscesses.

- Serum anti-coccidioidal antibodies are specific but not sensitive during the first 1–2 weeks after infection. Repeat testing can increase sensitivity. Diagnosis in the outpatient setting usually relies on serologic testing.
- PCR assays of respiratory specimens have been developed that are highly sensitive and specific.

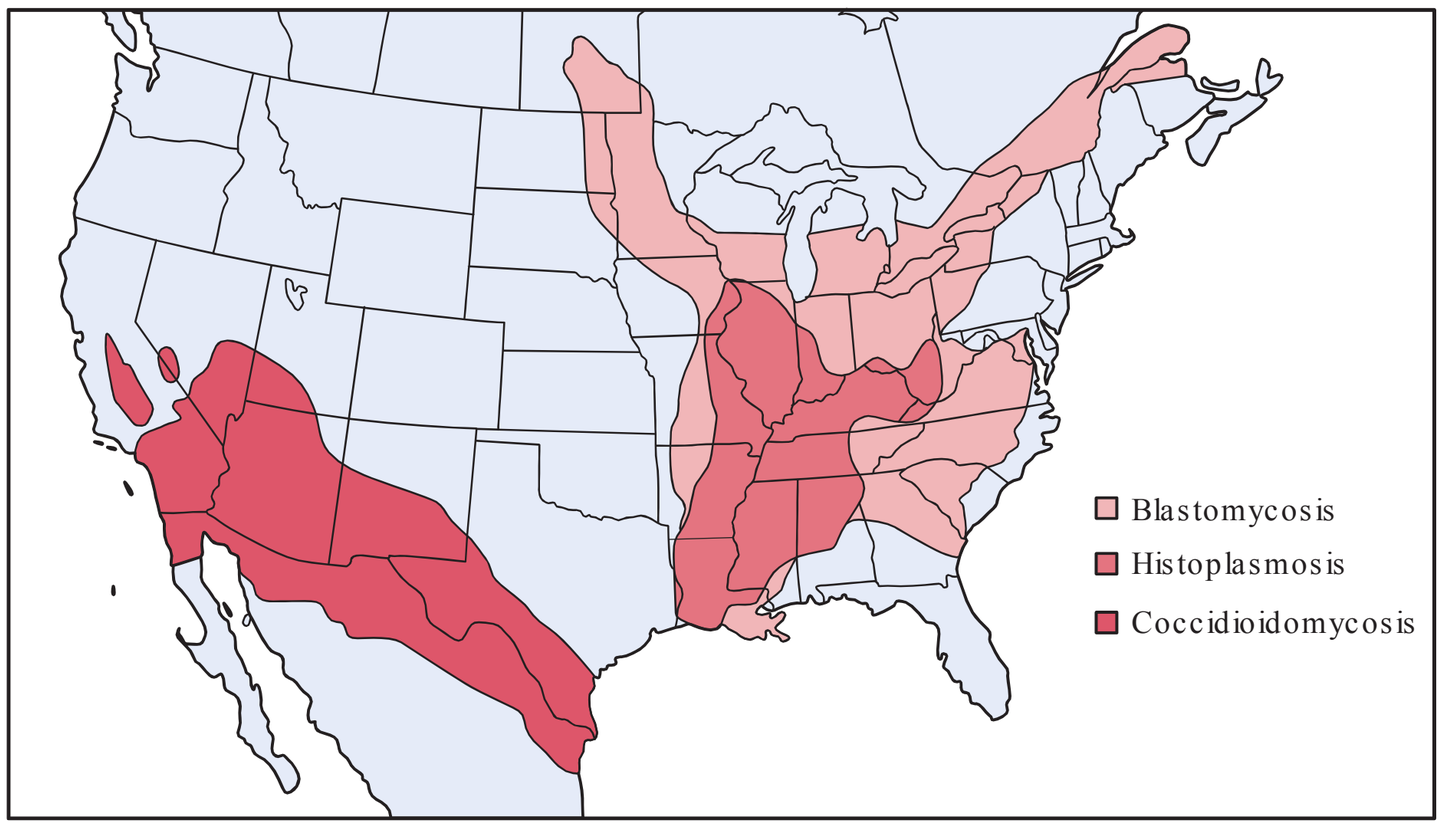


FIGURE 2.8-8. Geographic distribution of systemic fungal infection in the United States. (Reproduced with permission from Ryan KJ, Ray CG. Sherris Medical Microbiology, 5th ed. New York, NY: McGraw-Hill; 2010.)

- Obtain bronchoalveolar lavage as well as fungal cultures of sputum, wound exudate, or other affected tissue. Cultures are usually only obtained in hospitalized patients or patients with severe disease, and growth can take days to weeks.
- Identify Coccidioides immitis spherules on H&E or other special sputum or tissue stains.
- CXR findings may be normal or may show infiltrates, nodules, cavities, mediastinal or hilar adenopathy, or pleural effusion.
- Consider bronchoscopy, fine-needle biopsy, open lung biopsy, or pleural biopsy if serology is indeterminate.

KEY FACT

Consider coccidioidomycosis in a patient from the southwestern United States who presents with respiratory infection. HIV-⊕, Filipino, black, and pregnant patients are at increased risk of dissemination.

Treatment

- **Acute:** PO fluconazole or itraconazole can be used for mild infection or continuation therapy once the patient is stable. IV therapy is rarely necessary; however, consider **IV amphotericin B** for severe or protracted 1° pulmonary infection and disseminated disease.
- **Chronic:** No treatment is needed for asymptomatic chronic pulmonary nodules or cavities. Progressive cavitary or symptomatic disease usually requires surgery plus long-term azole therapy for 8–12 months.

INFLUENZA

A highly contagious orthomyxovirus transmitted by droplet nuclei. There are three types of influenza: A, B, and C. Subtypes of influenza A (eg, H5N1, H1N1) are classified on the basis of glycoproteins (hemagglutinin and neuraminidase). Relevant terms are as follows:

- **Antigenic drift:** Refers to **small, gradual changes in surface proteins through point mutations.** These small changes are sufficient to allow the virus to escape immune recognition, accounting for the fact that **individuals can be infected with influenza multiple times.**
- **Antigenic shift:** Describes an **acute, major change in the influenza A subtype** (significant genetic reassortment) circulating among humans; **leads to pandemics.**

In the United States, the typical influenza season begins in November and lasts until March. **Yearly vaccination with inactivated influenza virus is currently recommended for all patients ≥ 6 months of age.** Children 6 months to 9 years of age require two doses of the seasonal vaccine if they are receiving the vaccine for the first time. A high-dose flu vaccine is available for people ≥ 65 years of age.

History/Pe

Patients typically present with abrupt onset of **fevers, myalgias, chills, cough, coryza,** and weakness. Elderly patients may have atypical presentations characterized only by confusion.

Diagnosis

Best initial step in management: Rapid influenza test of viral antigens from nasopharyngeal swab. More definitive diagnosis can be made with DFA tests, viral culture, or PCR assays. Rapid influenza tests have low sensitivity, and influenza is usually a clinical diagnosis. Leukopenia is a common finding.

KEY FACT

A live attenuated, nasally delivered influenza vaccine is available for healthy people 2–49 years of age who are not pregnant or severely immunocompromised.

Treatment

- Symptomatic care with analgesics and cough medicine.
- Antivirals such as oseltamivir or zanamivir are most effective when used **within 2 days of onset** and may shorten the duration of infection by 1–3 days.

Complications

Severe 1° viral pneumonia, 2° bacterial pneumonia (see "Postviral" in Table 2.8-2), sinusitis, bronchitis, and exacerbation of COPD and asthma can occur.

CNS Infections

MENINGITIS

Acute bacterial meningitis is a **life-threatening** emergency. Viral (also called "aseptic") meningitis is more common and clinically less morbid. Risk factors for meningitis include recent ear infection, sinusitis, immunodeficiencies, recent neurosurgical procedures, crowded living conditions (ie, college dorms, military), and sick contacts. Causes by age group are listed in Table 2.8-5.

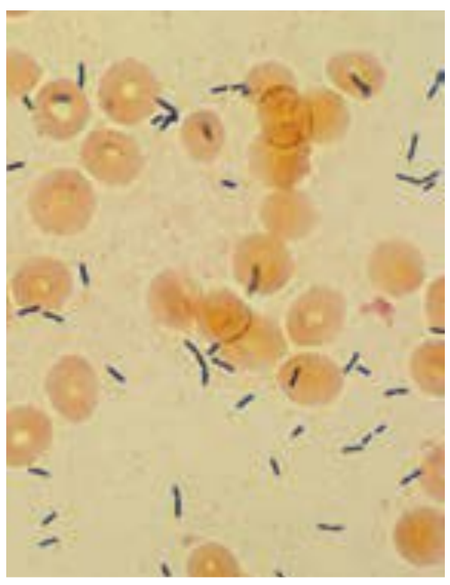


FIGURE 2.8-9. Listeria. These numerous rod-shaped bacilli were isolated from the blood of a patient with Listeria meningitis.

TABLE 2.8-5. Causes of Meningitis by Age Group[a,b]

Newborn (0–6 Months)	Children (6 Months–6 years)	6–60 years	60 years +
GBS	Spneumoniae	Nmeningitidis (#1 in teens)	Spneumoniae
Ecoli/GNRs	Neisseria meningitidis	Spneumoniae	GNRs
Listeria (see Figure 2.8-9).	Hinfluenza serotype b	Enteroviruses	Listeria
	Enteroviruses	HSV	Nmeningitidis

[a]Causes in HIV include Cryptococcus spp., CMV, HSV, VZV, TB, toxoplasmosis (brain abscess), and JC virus (progressive multifocal leukoencephalopathy, PML).

[b]The incidence of Hinfluenzae meningitis has greatly ↓ over the past 10–15 years as a result of the Hinfluenza vaccine.

History/Pe

About half of patients present with classic triad of **fever, headache, and neck stiffness.** Other symptoms include malaise, **photophobia,** altered mental status, **nausea/vomiting,** seizures, or signs of meningeal irritation (⊕ Kernig and Brudzinski signs).

Diagnosis

- Obtain a **lumbar puncture (LP)** for **CSF Gram stain, and culture ideally before initiation of antibiotics;** obtain glucose, protein, WBC count plus differential, RBC count, and opening pressure (in the absence of papilledema or focal neurologic deficits).
- **Viral PCRs** (eg, HSV); **cryptococcal antigen** (for HIV patients).
- **CT or MRI** is indicated in a minority of patients before LP, in particular those with altered mental status, papilledema, or focal neurologic deficits to exclude a mass lesion or increased intracranial pressure. If CT is being obtained, empiric antibiotics should be started beforehand. Obtain blood cultures. CBC may reveal leukocytosis; CSF findings vary (see Table 2.8-6).

Treatment

- Antibiotics should be administered rapidly (see Table 2.8-7) and can be given empirically up to 2 hours before an LP.
- Some cases of viral meningitis can be treated with supportive care and close follow-up.

KEY FACT

Apetechial or purpuric rash is characteristic of meningococcal meningitis. Waterhouse-Friderichsen syndrome (adrenal insufficiency due to bleeding into the adrenal gland) is characterized by profound hypotension and has high mortality.

KEY FACT

Acute bacterial meningitis is a life-threatening emergency. Antibiotics should be started as soon as possible.

TABLE 2.8-6. CSF Profile

	RBCs (per MM^3)	WBCs (per MM^3)	Glucose (Mg/dl)	Protein (Mg/dl)	Opening Pressure ($cM H_2O$)	Appearance	Gamma Globulin (% protein)
Normal	< 10	< 5	~ 2/3 of serum	15–45	10–20	Clear	3–12
Bacterial meningitis	↔	↑ (> 1000 PMNs)	↓	↑	↑	Cloudy/ purulent	↔ or ↑
Viral meningitis	↔	↑ (monos/ lymphs)	↔	↔ or ↑	↔ or ↑	Most often clear	↔ or ↑
Aseptic meningitis	↔	↑	↔	↔ or ↑	↔	Clear	↔
Subarachnoid hemorrhage	↑↑	↑	↔	↑	↔ or ↑	Yellow/red	↔ or ↑
Guillain-Barré syndrome	↔	↔	↔ or ↑	↑↑	↔	Clear or yellow (high protein)	↔
MS	↔	↔ or ↑	↔	↔	↔	Clear	↑↑
Pseudotumor cerebri	↔	↔	↔	↔	↑↑↑	Clear	↔

TABLE 2.8-7. Empiric Treatment of Bacterial Meningitis

Age	Causative Organism	Treatment
< 1 month	GBS, Ecoli/GNRs, Listeria.	Ampicillin + cefotaxime or gentamicin.
1–3 months	Pneumococci, meningococci, Hinfluenza .	Vancomycin IV+ ceftriaxone or cefotaxime.
3 months to adulthood	Pneumococci, meningococci.	Vancomycin IV+ ceftriaxone or cefotaxime.
> 60 years/alcoholism/ chronic illness	Pneumococci, gram-⊖ bacilli, Listeria, meningococci.	Ampicillin + vancomycin + cefotaxime or ceftriaxone.

KEY FACT

Although other medications may be used, rifampin and ciprofloxacin are the most frequently used prophylaxis of choice for close contacts of patients with meningococcal meningitis.

- Close contacts of patients with meningococcal meningitis should receive **rifampin, ciprofloxacin,** or ceftriaxone.
- **Dexamethasone** ↓ mortality, hearing loss, and short-term neurologic complications in bacterial meningitis caused by S pneumoniae, if given 15–20 minutes before antibiotics.
- If immunocompromised, elderly, or neonate, add ampicillin for Listeria.

Complications

Sensorineural hearing loss, mental impairment, seizures, cerebral edema, and ↑ intracranial pressure (ICP), subdural empyema, subdural effusions, brain abscess, ventriculitis/hydrocephalus, focal neurologic deficits (eg, cranial nerve palsies), hyponatremia, coma, death.

KEY FACT

The presence of RBCs in CSF without a history of trauma is highly suggestive of HSV encephalitis.

ENCEPHALITIS

HSV and **arboviruses** are the most common causes of encephalitis. Rarer etiologies include CMV, toxoplasmosis, West Nile virus, VZV, Borrelia, Rickettsia, Legionella, enterovirus, Mycoplasma, and cerebral malaria. Children and the elderly are the most vulnerable.

KEY FACT

CNS infections key words:
- Photophobia, nuchal rigidity = meningitis.
- Focal neurologic deficits = brain abscess.
- Confusion, mental status changes = encephalitis.

History/Pe

- Presents with **altered consciousness, headache, fever, and seizures.** Lethargy, confusion, coma, and focal neurologic deficits (cranial nerve deficits, accentuated DTRs) may also be present.
- The differential includes brain abscess, malignancy, toxic-metabolic encephalopathy, subdural hematoma, and subarachnoid hemorrhage.

KEY FACT

HSV encephalitis is associated with high morbidity. PCR is highly sensitive and specific. IV acyclovir should be started ASAP if this diagnosis is suspected.

Diagnosis

- CSF shows lymphocytic pleocytosis and moderately ↑ protein. The glucose level is low in tuberculous, fungal, bacterial, and amebic infections.
- Obtain a LP for cell count, glucose, protein, culture for bacteria, fungi, and mycobacteria, Gram stain (bacteria), acid-fast stain (mycobacteria), India ink stain (Cryptococcus). Order a **PCR** for HSV, CMV, EBV, VZV, and enterovirus. Obtain West Nile IgM serologies. Consider a wet preparation (free-living amebae) and a Giemsa stain (trypanosomes) if the history is suggestive.
- **CT or MRI** may demonstrate characteristic **temporal lobe signal abnormalities in HSV encephalitis** (see Figure 2.8-10).

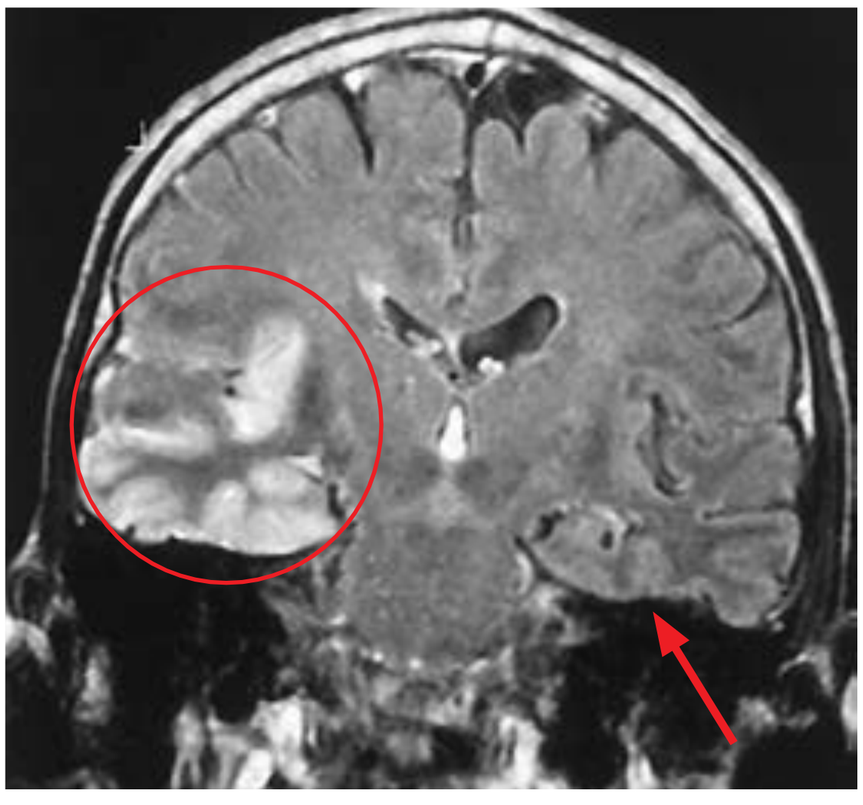


FIGURE 2.8-10. HSV encephalitis. Coronal FLAIR image of a young man with HSV encephalitis shows the characteristic MRI pattern within the cortex of the right temporal lobe (circle). The left temporal lobe is also involved (arrow), but to a lesser extent. (Reproduced with permission from Fauci AS et al. Harrison's Principles of Internal Medicine, 17th ed. New York, NY: McGraw-Hill; 2008.)

Treatment

- **HSV encephalitis:** Requires immediate IV acyclovir.
- **CMV encephalitis:** Treat with IV ganciclovir ± foscarnet.
- Give doxycycline for suspected Rocky Mountain spotted fever or ehrlichiosis. Treat Lyme encephalitis with ceftriaxone.

BRAIN ABSCESS

A focal, suppurative infection of the brain parenchyma, usually with a **"ring-enhancing"** appearance due to fibrous capsule (see Figure 2.8-11). The most common pathogens are **streptococci, staphylococci,** and **anaerobes; multiple** organisms are often implicated (80–90% are polymicrobial). Nonbacterial causes include Toxoplasma and Candida; Aspergillus and zygomycosis should be considered in immunocompromised hosts, and neurocysticercosis should be considered in relevant epidemiologic settings (Central and South America, sub-Saharan Africa and Asia). Modes of transmission include the following:

- **Direct spread:** Due to paranasal sinusitis (10% of cases; frequently affects young men, and often due to Streptococcus milleri), **otitis media** or **mastoiditis** (33%), or **dental infection** (2%).
- **Direct inoculation:** Affects patients with a history of head trauma or neurosurgical procedures.
- **Hematogenous spread** (25% of cases): Often shows a **middle cerebral artery distribution** with **multiple abscesses** that are poorly encapsulated and located at the **gray-white junction.**

History/Pe

- **Headache,** drowsiness, inattention, confusion, and **seizures** are early symptoms, followed by signs of **increasing ICP** and then a **focal neurologic deficit.**
- **Headache is the most common symptom and is often dull, constant, and refractory to treatment. ↑ ICP** leads to **CN III and CN VI deficits.**

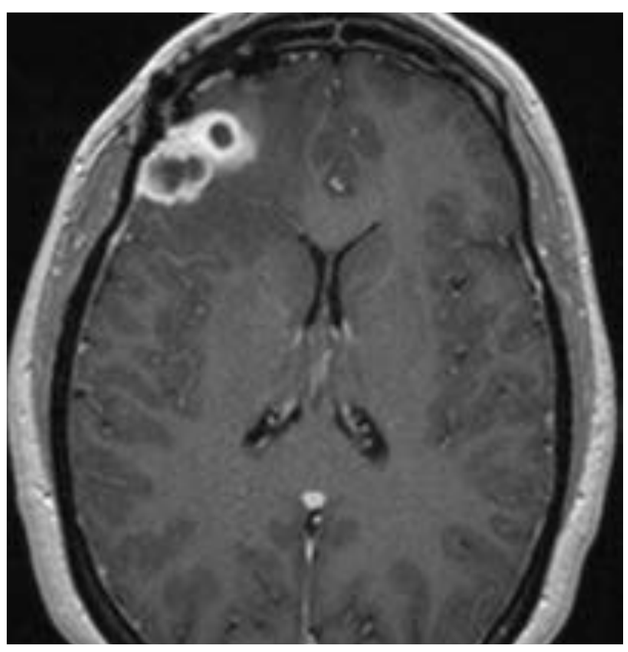


FIGURE 2.8-11. Brain abscess. Post contrast MRI of the brain shows ring-enhancing lesions in the lateral right frontal lobe, with "daughter" lesions (smaller adjacent rings of enhancement) also noted. (Reproduced with permission from USMLE-Rx.com.)

Q

A 70-year-old man presents to the ED in February with a high fever and a productive cough. One week ago he was treated for influenza, and his symptoms improved until 3 days ago, when they returned with greater severity. Examination now reveals cyanosis, tactile fremitus, and dullness to percussion over the left lower lobe. Against what organism should antibiotic therapy be directed?

KEY FACT

The classic clinical triad of **headache, fever, and a focal neurologic defici** is present in 50% of cases of brain abscess.

KEY FACT

When fever is absent, 1° and metastatic brain tumors should be considered in the dif erential diagnosis.

KEY FACT

In general, **do not** perform LP on a patient with a mass lesion in the brain in light of the risk of uncal herniation.

Diagnosis

- **CT scan** will show a **ring-enhancing lesion** with a low-density core. MRI has higher sensitivity for early abscesses and posterior fossa lesions.
- **CSF analysis** is not necessary and **may precipitate brainstem herniation.**
- Lab values may show peripheral leukocytosis, ↑ erythrocyte sedimentation rate **(ESR),** and ↑ C reactive protein **(CRP).**

Treatment

- **Initiate broad-spectrum IV antibiotics** and **surgical drainage** (aspiration or excision) if necessary for diagnostic and/or therapeutic purposes. Lesions < 2 cm can often be treated medically.
- Administer a third-generation cephalosporin + metronidazole ± vancomycin; give IV therapy for 6–8 weeks. Obtain serial CT/MRIs to follow resolution.
- **Dexamethasone** with taper may be used in severe cases to ↓ cerebral edema; **IV mannitol** may be used to ↓ ICP. Give prophylactic anticonvulsants.

Human Immunodeficiency Viru

A retrovirus that targets and destroys CD4+ T lymphocytes. Infection is characterized by a high rate of viral replication that leads to a progressive decline in CD4+ count (see Figure 2.8-12).

- **CD4+ count:** Indicates the **degree of immunosuppression;** guides therapy and prophylaxis, and helps determine prognosis.
- **Viral load:** May predict the **rate** of disease progression; provides indications for treatment and gauges response to antiretroviral therapy (ART).

History/Pe

- Acute HIV infection (acute infection/seroconversion, acute retroviral syndrome) occurs days to weeks after exposure. The initial infection is often **asymptomatic,** but patients may also present with **mononucleosis-like or flulike symptoms** (eg, fever, lymphadenopathy, maculopapular rash, pharyngitis, diarrhea, nausea/vomiting, weight loss, headache).
- HIV infection can later present as night sweats, weight loss, thrush (see

A

Saureus. Postviral pneumonia is an important complication of influenza, especially in the elderly. Staphylococcus is the most common organism responsible for early bacterial superinfection, presenting just days after the onset of influenza. Necrotizing bronchopneumonia with cavitation and abscess formation is characteristic.

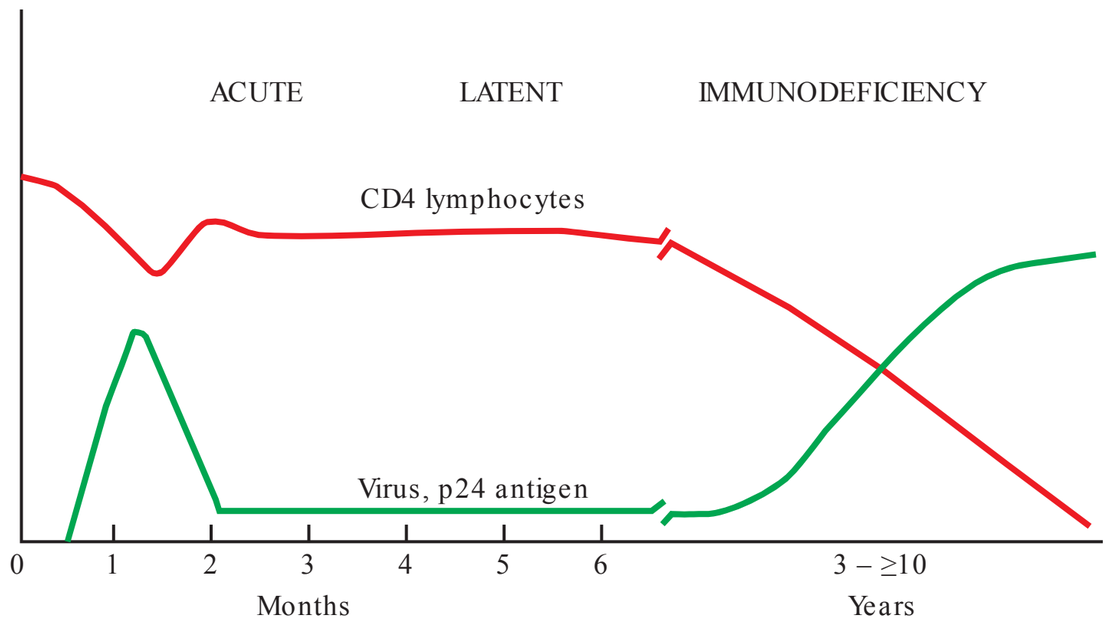


FIGURE 2.8-12. Time course of HIV infection. Note that the level of CD4 lymphocytes (red curve) remains normal for many years but then declines, resulting in the immunodeficiency stage, which is characterized by opportunistic infections and malignancies.

Figure 2.8-13), recurrent infections, or opportunistic infections. Complications are inversely correlated with CD4+ count (see Figure 2.8-14).

Diagnosis

- **ELISA test** (high sensitivity, moderate specificity): Detects anti-HIV antibodies in the bloodstream (can take up to 6 months to appear after exposure).
- **Western blot** (low sensitivity, high specificity): Confirmatory.
- **Rapid HIV tests** are now available.
- Baseline evaluation should include HIV RNA PCR (viral load), CD4+ cell count, CXR, PPD skin test or interferon-gamma release assay, Pap smear, mental status exam, VDRL/RPR, and serologies for CMV, viral hepatitis, toxoplasmosis, and VZV.
- Evaluation for acute retroviral syndrome (acute HIV) should include **HIV RNA PCR** (viral load); ELISA may be ⊖.

Treatment

- ART should be offered to all HIV-infected patients, regardless of symptoms (presence of AIDS-defining illness or HIV-related conditions) and CD4 count. Evidence for decreased morbidity and mortality is most well established in patients with CD4 < 500. Patients should be informed of the benefits and potential risks of early treatment, importance of adherence, and commit to lifelong therapy.
- The initial regimen should generally consist of a combination of two nucleoside/nucleotide reverse transcriptase inhibitors (RTIs) plus either one non-nucleoside RTI or one protease inhibitor or one integrase inhibitor. **The most important principle is to select multiple medications**

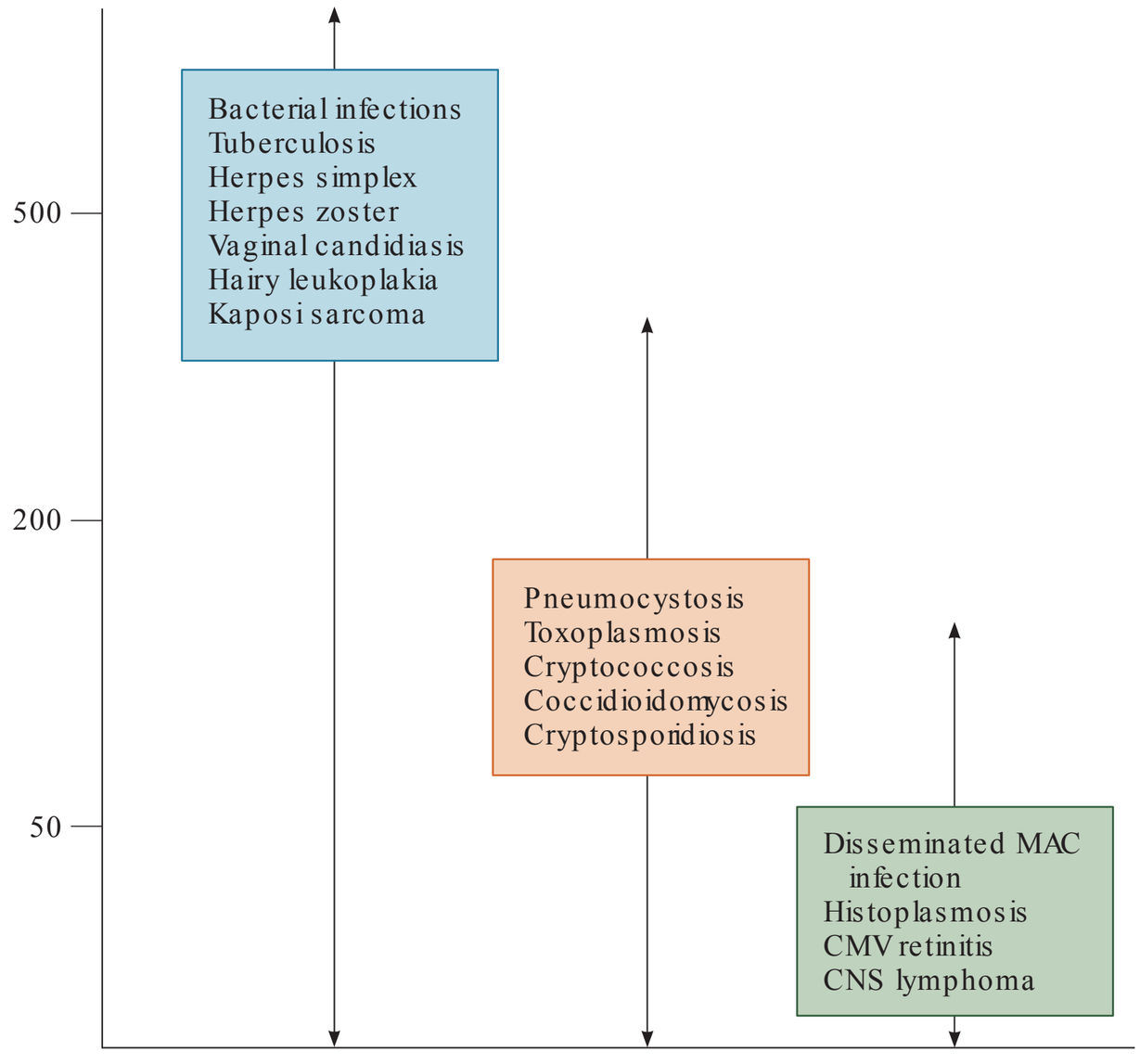


FIGURE 2.8-14. Relationship of CD4+ count to development of opportunistic infections. (Reproduced with permission from McPhee SJ et al. Current Medical Diagnosis & Treatment 2011. New York, NY: McGraw-Hill; 2011.)



FIGURE 2.8-13. Oral thrush in HIV-positive patient. (Used with permission of Drs. John Molinari and Sol Silverman, Jr., Centers for Disease Control and Prevention, Atlanta, GA)

KEY FACT

Common AIDS-defining illnesses

- Esophageal candidiasis.
- CMV retinitis.
- Kaposi sarcoma (human herpesvirus-8) (see Figure 2.8-15).
- CNS lymphoma, toxoplasmosis, PML.
- P jirovecii pneumonia or recurrent bacterial pneumonia.
- HIV encephalopathy.
- Disseminated mycobacterial or fungal infection.
- Invasive cervical cancer.

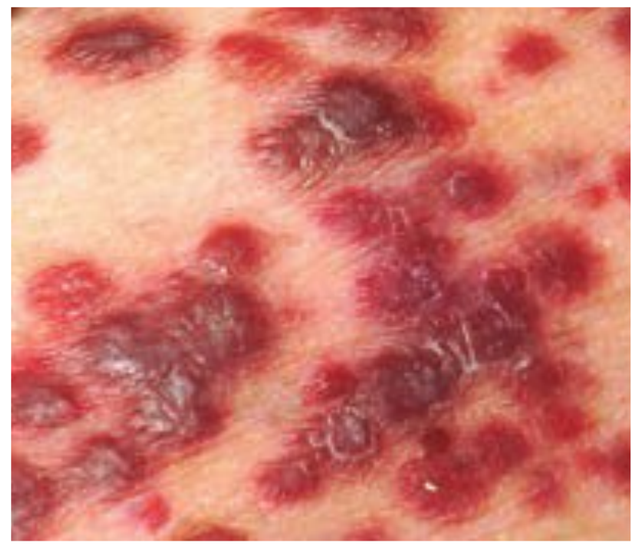


FIGURE 2.8-15. Kaposi sarcoma (HHV-8). A neoplasm of endothelial cells seen in HIV/AIDS and transplant patients. (Reproduced with permission from the US Department of Health and Human Services.)

KEY FACT

If a pregnant HIV-⊕ patient is not on ART at the time of delivery, she should be treated with zidovudine (AZT) intrapartum. Infants should receive AZT for 6 weeks after birth.

KEY FACT

Common side effects of HIV medications:

- Protease inhibitors—hyperglycemia, hyperlipidemia, lipodystrophy.
- Nucleoside RTIs—Bone marrow suppression, neuropathy.
- Indinavir—crystal-induced nephropathy, nephrolithiasis.
- Didanosine—pancreatitis.
- Abacavir—hypersensitivity reaction.
- Nevirapine—liver failure.
- Efavirenz—vivid dreams, hallucinations.

KEY FACT

MMR and varicella vaccines are the only live vaccines that should be given to HIV patients (if CD4 > 200). Do not give oral polio vaccine to HIV-⊕ patients or their contacts.

(usually at least three) in order to achieve a durable treatment response and limit the emergence of resistance.

- The goal of therapy is complete viral suppression (< 50 viral copies). After therapy is started, CD4+ count and viral load should be monitored monthly until suppression is achieved and every 3–6 months afterward.
- An HIV genotype should be obtained before the initiation of therapy and when resistance is suspected, as such testing can provide mutation information and identify resistance to specific antiretrovirals.
- The recommended prophylaxis for HIV exposure varies according to the severity of the source infection and the exposure. In the setting of a percutaneous injury, mucous membrane exposure, or nonintact skin exposure with an HIV-⊕ source, begin ART as soon as possible with a basic two-drug regimen or an expanded regimen of three or more drugs for 4 weeks, depending on the severity of the source infection.

Table 2.8-8 outlines prophylactic measures against opportunistic infections.

Opportunistic Infections

Figure 2.8-16 illustrates the microscopic appearance of some common opportunistic organisms.

TABLE 2.8-8. Prophylaxis for HIV-Related Opportunistic Infection

Pathogen	Indication For Prophylaxis	Treatment	Notes
P jirovecii pneumonia	CD4+ < 200/mm^3, prior P jirovecii infection.	Single-strength TMP-SMX.	Discontinue prophylaxis when CD4+ is > 200/mm^3 for ≥ 3 months.
Mycobacterium avium complex (MAC)	CD4+ < 50–100/mm^3.	Weekly azithromycin.	Discontinue prophylaxis when CD4+ is > 100/mm^3 for > 6 months.
Toxoplasma gondii	CD4+ < 100/mm^3 + ⊕ IgG serologies.	Double-strength TMP-SMX.	—
M tuberculosis	PPD > 5 mm or "high risk" (see TB section).	INH × 9 months (+ pyridoxine) or rifampin × 4 months.	Include pyridoxine with INH-containing regimens.
Candida	Multiple recurrences.	**Esophagitis:** Fluconazole. **Oral:** Fluconazole or nystatin swish and swallow.	—
HSV	Multiple recurrences.	Daily suppressive acyclovir, famciclovir, or valacyclovir.	—
S pneumoniae	All patients.	Pneumovax.	Give every 5 years provided that CD4+ is > 200/mm^3.
Influenz	All patients.	Influenza accine annually.	—

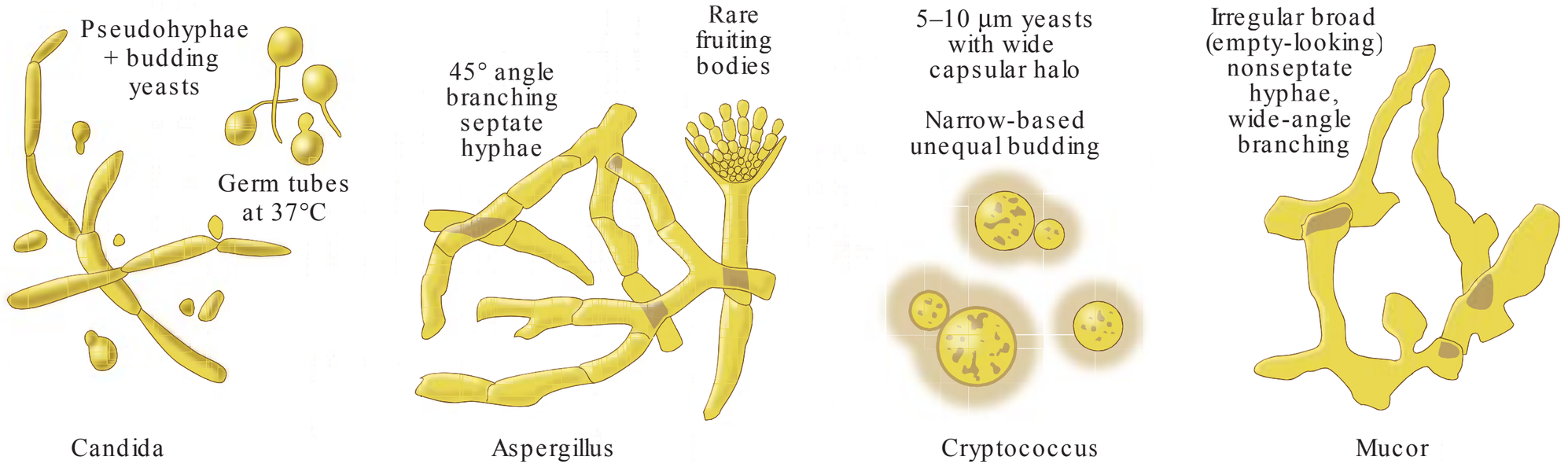


FIGURE 2.8-16. Common opportunistic organisms.

OROPHARYNGEAL CANDIDIASIS (THRUSH)

- **Risk factors:** Xerostomia, antibiotic use, denture use, and immunosuppression (eg, HIV, leukemias, lymphomas, cancer, diabetes, corticosteroid inhaler use, immunosuppressive treatment).
- **Hx/PE:** Presents with **soft white plaques that can be rubbed off,** with an erythematous base and possible mucosal burning. The differential diagnosis includes oral hairy leukoplakia (affects the lateral borders of the tongue; not easily rubbed off). Odynophagia is characteristic of candidal esophagitis.
- **Dx:** Usually clinical. KOH or Gram stain shows **budding yeast and/or pseudohyphae.**
- **Tx:** Treat thrush with local therapy (eg, nystatin suspension, clotrimazole tablets, or a PO azole such as fluconazole). Treat candidal esophagitis with PO azole therapy.

CRYPTOCOCCAL MENINGITIS

- **Risk factors:** Include AIDS and exposure to **pigeon droppings.**
- **Hx/PE:** Presents with headache, fever, impaired mentation, signs of increased ICP, and **absent meningeal signs.** The differential includes toxoplasmosis, lymphoma, TB meningitis, AIDS dementia complex, PML, HSV encephalitis, and other fungal disease.
- **Dx: LP** (↓ CSF glucose; ↑ protein; ↑ leukocyte count with monocytic predominance, ↑↑ opening pressure); ⊕ **cryptococcal antigen testing in CSF and/or blood, CSF India ink stain,** and fungal culture.
- **Tx:**
  - **IV amphotericin B** + flucytosine × 2 weeks; then fluconazole × 8 weeks. Lifelong **maintenance therapy** should be administered with fluconazole until symptoms resolve and CD4+ is > 100/mm^3 for > 1 year.
  - ↑ opening pressure may require serial LPs or a ventriculoperitoneal shunt for management.

HISTOPLASMOSIS

Risk factors include HIV/AIDS, spelunking, and exposure to bird or bat excrement, especially in the **Ohio** and **Mississippi** river valleys (see Figure 2.8-8).

MNEMONIC

AIDS pathogens—

The Major Pathogens Concerning Complete T-Cell Collapse

Toxoplasma gondii
Mycobacterium avium–intracellulare
Pneumocystis jirovecii
Candida albicans
Cryptococcus neoformans
Tuberculosis
CMV
Cryptosporidium parvum

KEY FACT

The CSF antigen test for cryptococcal meningitis is highly sensitive and specific.

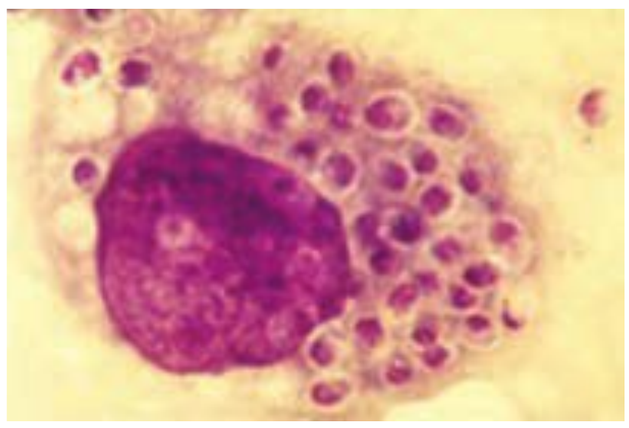


FIGURE 2.8-17. Histiocyte macrophage containing numerous yeast cells of Histoplasma capsulatum **(Giemsa stain).** (Used with permission of Dr. DT McClenan, Centers for Disease Control and Prevention, Atlanta, GA.)

KEY FACT

Nocardia is a partially acid-fast, gram-⊕, branching rod found in soil that is a common cause of lung and CNS infection in immunocompromised hosts. TMP-SMX is the treatment of choice (see Figure 2.8-18).

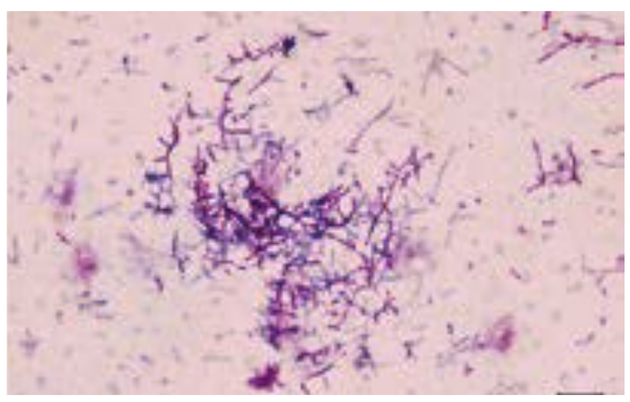


FIGURE 2.8-18. Nocardia. Branching filaments on acid-fast stain. (Adapted with permission from Leli C et al. Fatal Nocardia farcinica bacteremia diagnosed by matrix-assisted laser desorption-ionization time of flight mass spectrometry in a patient with myelodysplastic syndrome treated with corticosteroids. Case Rep Med. 2013;2013:368637.)

KEY FACT

Suspect P jirovecii pneumonia in any HIV patient who presents with a nonproductive cough and dyspnea.

History/Pe

- 1° exposure is often asymptomatic or causes a flulike illness.
- Presentation may range from no symptoms to fulminant disease with pulmonary and/or extrapulmonary manifestations.
- Fever, weight loss, hepatosplenomegaly, lymphadenopathy, a nonproductive cough, palatal ulcers, and pancytopenia indicate disseminated infection (most often within 14 days).
- The differential diagnosis includes atypical bacterial pneumonia, blastomycosis, coccidioidomycosis, TB, sarcoidosis, pneumoconiosis, and lymphoma.

Diagnosis

- **CXR** shows diffuse nodular densities, focal infiltrate, cavity, or hilar lymphadenopathy (chronic infection is usually cavitary).
- The **urine and serum polysaccharide antigen test** is the most sensitive test for making the initial diagnosis of disseminated disease, monitoring response to therapy, and diagnosing relapse. Culture is also diagnostic (blood, sputum, bone marrow, CSF).
- The yeast form is seen with special stains on biopsy (bone marrow, lymph node, liver) or bronchoalveolar lavage (see Figure 2.8-17).

Treatment

Depends on the severity of disease and the host:

- **Mild pulmonary disease or stable nodules:** Treat supportively in the immunocompetent host. Consider itraconazole.
- **Chronic cavitary lesions:** Give itraconazole for > 1 year.
- **Severe acute pulmonary disease or disseminated disease: Liposomal amphotericin B** or amphotericin B × 14 days followed by itraconazole × 1 year or longer. Lifelong maintenance therapy with daily itraconazole may be necessary.

PNEUMOCYSTIS JIROVECII PNEUMONIA

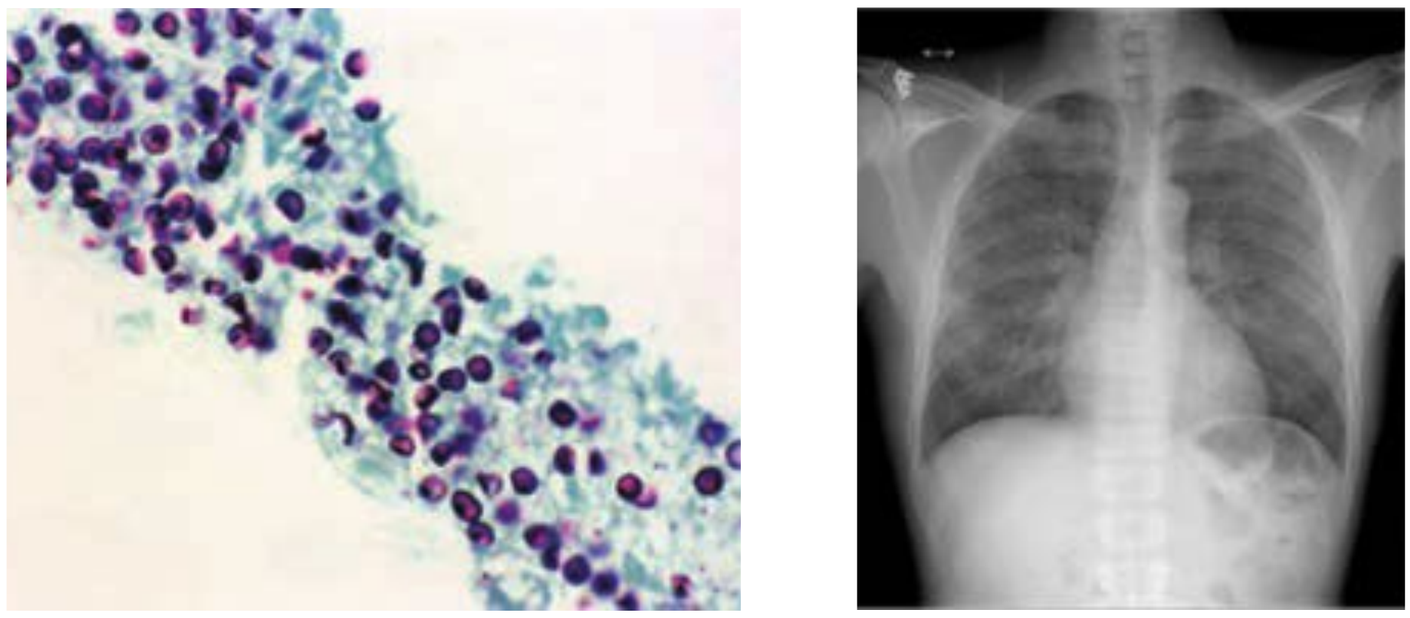
Formerly known as Pneumocystis carinii pneumonia, or PCP. Risk factors include impaired cellular immunity and AIDS.

History/Pe

- Presents with **dyspnea on exertion,** fever, a **nonproductive cough,** tachypnea, weight loss, fatigue, and **impaired oxygenation. Typically, symptoms have been present for weeks.**
- Can also present as disseminated disease or as local disease in other organ systems.
- The differential diagnosis includes TB, histoplasmosis, and coccidioidomycosis.

Diagnosis

- Diagnosed by cytology of induced sputum or bronchoscopy specimen with silver stain and immunofluorescence (see Figure 2.8-19A). Obtain an ABG to check Pa_{O_2}.
- CXR most commonly shows diffuse, bilateral interstitial infiltrates with a ground-glass appearance (see Figure 2.8-19B), but any presentation is possible.



A B

FIGURE 2.8-19. Pneumocystis **pneumonia. (A)** Lung tissue stained with silver uncovers folded cysts containing comma-shaped spores. **(B)** Frontal CXR shows diffuse "ground-glass" lung opacities characteristic of PCP in this patient with AIDS and a CD4+ count of 26. (Part A reproduced with permission from Ryan KJ, Ray CG. Sherris Medical Microbiology, 5th ed. New York, NY: McGraw-Hill; 2010. Part Breproduced with permission from USMLE-Rx.com.)

Treatment

- Treat with **high-dose** TMP-SMX × 21 days.
- A prednisone taper should be used in patients with moderate to severe hypoxemia (Pa_{O_2} < 70 mm Hg or an arterial-alveolar oxygen gradient > 35).

CYTOMEGALOVIRUS

Seventy percent of adults in the United States have been infected with CMV, and most are asymptomatic; reactivation generally occurs in immunocompromised patients.

- Transmission occurs via **sexual contact, vertical transmission, breast milk, respiratory droplets** in nursery or day care facilities, and **blood transfusions.**
- Risk factors for reactivation include the first 100 days status post tissue or bone marrow transplant and HIV/AIDS (CD4+ < 100/mm^3 or viral load > 10,000 copies).

History/Pe

- Systemic infection may resemble EBV mononucleosis (see the discussion of infectious mononucleosis).
- Specific manifestations include the following:
  - **CMV retinitis:** Associated with retinal detachment ("pizza pie" retinopathy); presents with floaters and visual field changes (CD4+ < 50/mm^3).
  - **GI and hepatobiliary involvement:** Can present with multiple nonspecific GI symptoms, including bloody diarrhea and abdominal pain. CMV, microsporidia, and cryptosporidia have been implicated in the development of **AIDS cholangiopathy.**
  - **CMV pneumonitis:** Presents with cough, fever, and sparse sputum production; associated with a high mortality rate. Much more common in patients with hematologic malignancies and transplant patients than in those with AIDS.
  - **CNS involvement:** Can include **polyradiculopathy, transverse myelitis,** and subacute **encephalitis** (CD4+ < 50/mm^3; periventricular calcifications).

Q 1

A 19-year-old college student is brought to the ED from her dorm room, where she was found by her roommate in a confused state. She complains of fever, nausea, vomiting, and pain in her neck and head. She has a petechial rash on her legs. CSF examination reveals a glucose level of 22 mg/dL, a protein level of 140 mg/dL, and a WBC count of 1400/mm^3. What is the most likely organism responsible for her condition?

Q 2

A 35-year-old HIV-infected man from Ohio presents to his primary care provider with low-grade fever, dry cough, malaise, and a 5-lb weight loss over the past month. He is adherent to his HIV medications. Physical examination shows hepatosplenomegaly and palatal ulcers. His CBC reveals pancytopenia, and a CXR shows hilar lymphadenopathy. What is the next most appropriate step in management?

KEY FACT

Treat CMV infection with ganciclovir or valganciclovir.

Diagnosis

Virus isolation, culture, **tissue histopathology, serum PCR.**

Treatment

Treat with **ganciclovir, valganciclovir,** or foscarnet. Treat underlying disease if the patient is immunocompromised.

MYCOBACTERIUM AVIUM COMPLEX

Ubiquitous organisms causing **pulmonary** and **disseminated** infection in several demographic groups. The 1° pulmonary form occurs in **apparently healthy nonsmokers (Lady Windermere syndrome);** a 2° pulmonary form affects patients with **preexisting pulmonary disease** such as COPD, TB, or CF. Disseminated infection occurs in AIDS patients with a **CD4+ < 50/mm³.**

History/Pe

- Disseminated M avium infection in AIDS is associated with **fever, weakness,** and **weight loss in patients who are not on highly active ART (HAART) or chemoprophylaxis for MAC.**
- Hepatosplenomegaly and lymphadenopathy are occasionally seen.
- Adrenal insufficiency is possible in the setting of adrenal infiltration.

Diagnosis

- Obtain mycobacterial **blood cultures** (⊕ in 2–3 weeks).
- Labs show anemia, hypoalbuminemia, and ↑ **serum alkaline phosphatase and LDH.**
- Biopsy of bone marrow, intestine, or liver reveals **foamy macrophages** with **acid-fast bacilli.** Typical granulomas may be absent in immunocompromised patients.

Treatment

Treat with **clarithromycin** and consider **HAART if drug-naive. Ethambutol ± rifabutin is second line.** Continue for > 12 months and until CD4+ is > 100/mm³ for > 6 months.

Prevention

Weekly azithromycin for those with a CD4+ < 50/mm³ or AIDS-defining opportunistic infection.

1 A

Neisseria meningitidis. Suspect meningococcal meningitis in a very ill patient with fever, headache, altered mental status, a **petechial rash** in the lower extremities, and a CSF profile indicative of bacterial meningitis.

TOXOPLASMOSIS

Risk factors include ingesting **raw or undercooked meat** and **changing cat litter.**

History/Pe

- 1° infection is usually asymptomatic.
- Reactivated toxoplasmosis occurs in immunosuppressed patients and may present in specific organs (brain, lung, and eye > heart, skin, GI tract, and liver).
- Encephalitis is common in seropositive AIDS patients. Classically, CNS lesions present with fever, headache, altered mental status, seizures, and focal neurologic deficits.

2 A

Liposomal amphotericin B followed by itraconazole. The patient has clinical features of disseminated histoplasmosis (fever, malaise, weight loss, pancytopenia, hepatosplenomegaly, palatal ulcers).

Diagnosis

- **Serology, PCR** (indicates exposure and risk for reactivation); tissue examination for histology, isolation of the organism in mice, or tissue culture.
- In the setting of CNS involvement, **obtain a CT scan** (see Figure 2.8-20) **(look for multiple isodense or hypodense ring-enhancing mass lesions)** or an **MRI** (has a predilection for the **basal ganglia;** more sensitive).

Treatment

- Induction with high-dose PO **pyrimethamine** + **sulfadiazine and leucovorin** (a folic acid analog to prevent hematologic toxicity) × 4–8 weeks; maintenance with a low-dose regimen until the disease has resolved clinically and radiographically.
- **TMP-SMX (Bactrim DS)** or pyrimethamine + dapsone can be used for prophylaxis in patients with a CD4+ count < 100/mm^3 and a ⊕ toxoplasmosis IgG.

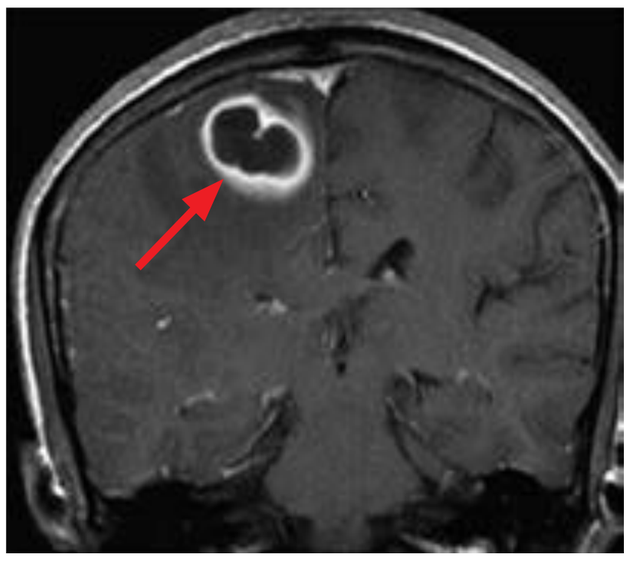


FIGURE 2.8-20. Toxoplasmosis. (Adapted with permission from Adurthi S et al. Utility of molecular and serodiagnostic tools in cerebral toxoplasmosis with and without tuberculous meningitis in AIDS patients: a study from South India. Ann Indian Acad Neurol 2010 Oct;13(4):263–270.)

Sexually Transmitted Diseases

CHLAMYDIA

The **most common bacterial STD in the United States.** Caused by Chlamydia trachomatis, which can infect the genital tract, urethra, anus, and eye. Risk factors include **unprotected sexual intercourse and new or multiple partners.** Often coexists with or mimics N gonorrhoeae infection (known as nongonococcal urethritis when gonorrhea is absent). LGV serovars of Chlamydia cause lymphogranuloma venereum, an emerging cause of proctocolitis.

History/Pe

- Infection is often asymptomatic in men and may present with **urethritis, mucopurulent cervicitis,** or **pelvic inflammatory disease (PID)** in women.
- Examination may reveal cervical/adnexal tenderness in women or penile discharge and testicular tenderness in men.
- The differential diagnosis includes gonorrhea, endometriosis, PID, orchitis, vaginitis, and UTI.
- **Lymphogranuloma venereum** presents in its 1° form as a **painless,** transient papule or shallow ulcer. In its 2° form, it presents as painful swelling of the inguinal nodes, and in its 3° form it can present as an "anogenital syndrome" (anal pruritus with discharge, rectal strictures, rectovaginal fistula, and elephantiasis).

Diagnosis

- Diagnosis is usually clinical; **culture** is the **gold standard.**
- **Urine tests (nucleic acid amplification test) are a rapid means of detection,** whereas DNA probes and immunofluorescence (for gonorrhea/chlamydia) take 48–72 hours.
- **Gram stain** of urethral or genital discharge may show **PMNs but no bacteria (intracellular).**

Treatment

- **Doxycycline** × 7 days or azithromycin once. Use azithromycin or amoxicillin in pregnant patients.
- **Treat sexual partners,** and maintain a low threshold to treat for N gonorrhoeae. LGV serovars require prolonged therapy for 21 days.

KEY FACT

Ring-enhancing lesions in patients with AIDS should always prompt consideration of toxoplasmosis and CNS lymphoma.

KEY FACT

Chlamydia infection is a common cause of nongonococcal urethritis in men.

KEY FACT

Chlamydia species cause arthritis, neonatal conjunctivitis, pneumonia, nongonococcal urethritis/PID, and LGV.

Q

A 27-year-old man with HIV presents to his primary-care physician with fever, night sweats, weight loss, and diarrhea. Today his CD4+ count is 25 cells/mm^3. A CBC is performed and is significant for anemia (a hemoglobin level of 8 mg/dL). Other labs show hypoalbuminemia and elevated alkaline phosphatase. What could have prevented this patient's condition?

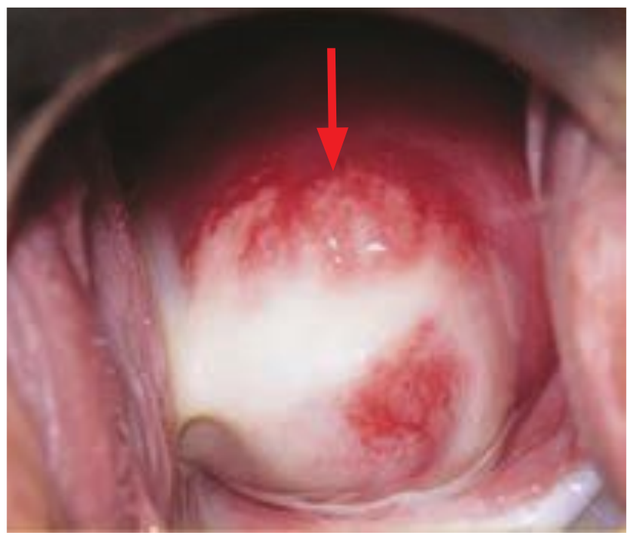


FIGURE 2.8-21. Purulent cervical discharge in pelvic inflammatory disease. (Adapted with permission from SOS-AIDS Amsterdam.)

Complications

- Chronic infection and pelvic pain, Reiter syndrome (urethritis, conjunctivitis, arthritis), Fitz-Hugh–Curtis syndrome (perihepatic inflammation and fibrosis). See Figures 2.8-21 and 2.8-22.
- Ectopic pregnancy/infertility can result from PID (in women) and epididymitis (in men).

GONORRHEA

A gram-⊖ intracellular diplococcus that can infect almost any site in the female reproductive tract. Infection in men tends to be limited to the urethra.

History/Pe

- Presents with a **greenish-yellow discharge,** pelvic or **adnexal pain,** and swollen Bartholin glands. Men experience a **purulent urethral discharge,** dysuria, and erythema of the urethral meatus.
- The differential diagnosis includes chlamydia, endometriosis, pharyngitis, PID, vaginitis, UTI, salpingitis, and tubo-ovarian abscess.

Diagnosis

- **Gram stain and culture** is the gold standard for any site (pharynx, cervix, urethra, or anus). **Nucleic acid amplification tests** can be sent on penile/vaginal tissue or from urine.
- Disseminated disease may present with **monoarticular septic arthritis,** rash, and/or **tenosynovitis.** See Figures 2.8-23 and 2.8-24.

Treatment

KEY FACT

Treat gonorrhea with two agents because of the high prevalence of resistance.

- **Ceftriaxone IM** and **azithromycin PO (regardless of whether chlamydia is present).** Condoms are effective prophylaxis. Treat the sexual partner or partners if possible. Fluoroquinolones should not be used because of emerging resistance.
- Disseminated disease requires IV ceftriaxone for at least 24 hours.

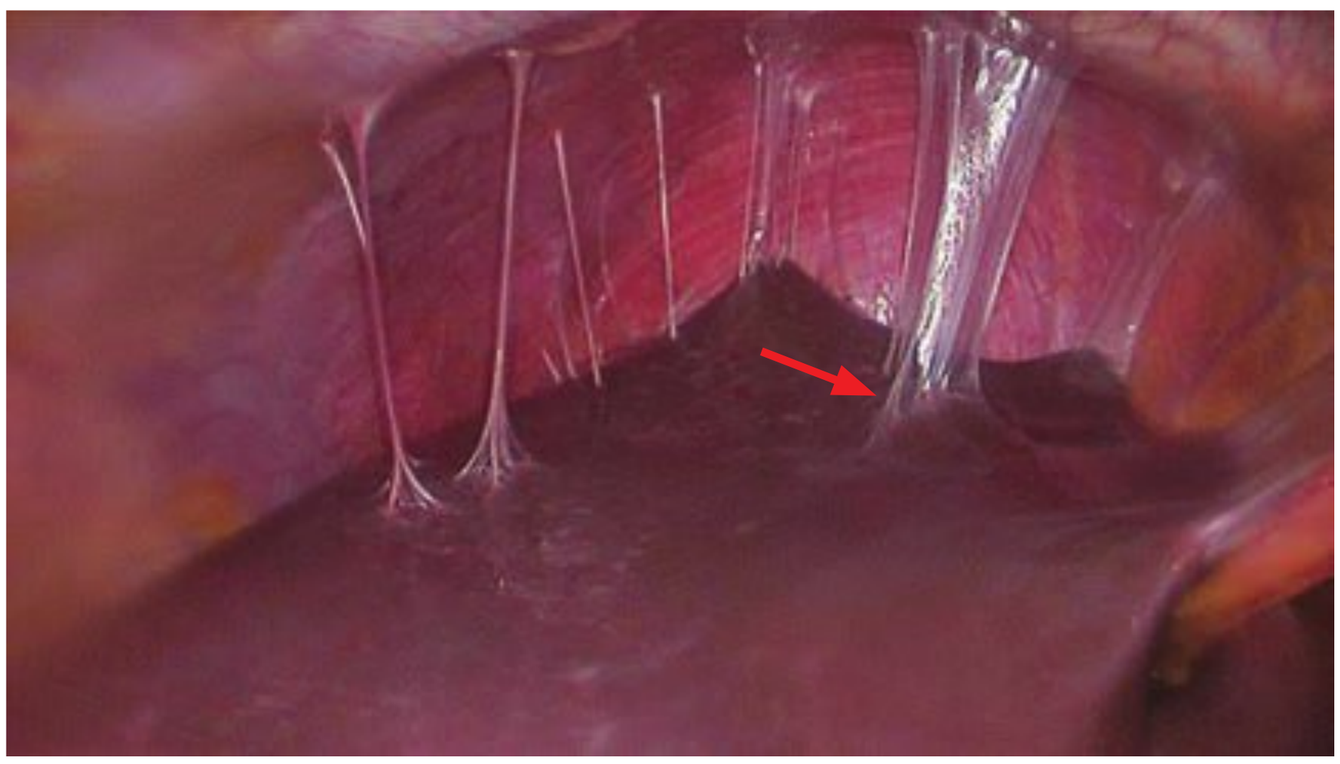


FIGURE 2.8-22. Adhesions in Fitz-Hugh–Curtis syndrome (PID). Note the adhesions (arrow) extending from the peritoneum to the surface of the liver. (Reproduced with permission from Hic et nunc.)

A

Azithromycin. The patient has signs and symptoms of disseminated Mycobacterium avium complex. HIV-infected patients with **CD4+ counts < 50 cells/mm^3** should receive prophylaxis against MAC with azithromycin once a week.



FIGURE 2.8-23. Disseminated gonococcal infection. Hemorrhagic, painful pustules are seen on erythematous bases. (Reproduced with permission from Wolf K et al. Fitzpatrick's Dermatology in General Medicine, 7th ed. New York, NY: McGraw-Hill; 2008.)

Complications

Persistent infection with pain; infertility; tubo-ovarian abscess with rupture; disseminated gonococcal infection (characterized by migratory polyarthralgia, tenosynovitis, and pustular skin lesions) (see Figure 2.8-24).

SYPHILIS

Caused by Treponema pallidum, a spirochete. AIDS can accelerate the course of disease progression.

History/Pe

- **1° (10–90 days after infection):** Presents with a **painless ulcer** (**chancre;** see Figure 2.8-25A).
- **2° (4–8 weeks after chancre):** Presents with low-grade fever, headache, malaise, and generalized lymphadenopathy with a diffuse, symmetric, asymptomatic (nonpruritic) **maculopapular rash on the soles and palms** (see Figure 2.8-25C, D). Highly infective 2° eruptions include mucous patches or **condylomata lata** (see Figure 2.8-26). Meningitis, hepatitis, nephropathy, and eye involvement may also be seen.

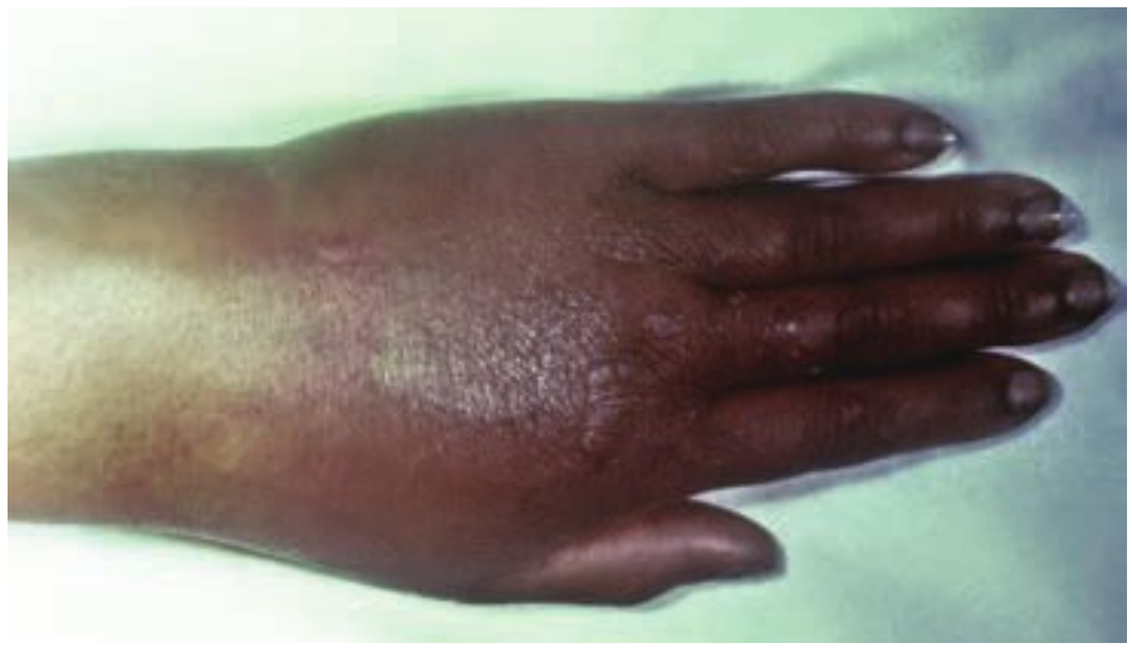


FIGURE 2.8-24. Neisseria gonorrhoeae **joint infection.** (Used with permission of Susan Lindsley, Public Health Image Library, Centers for Disease Control and Prevention, Atlanta, GA.)

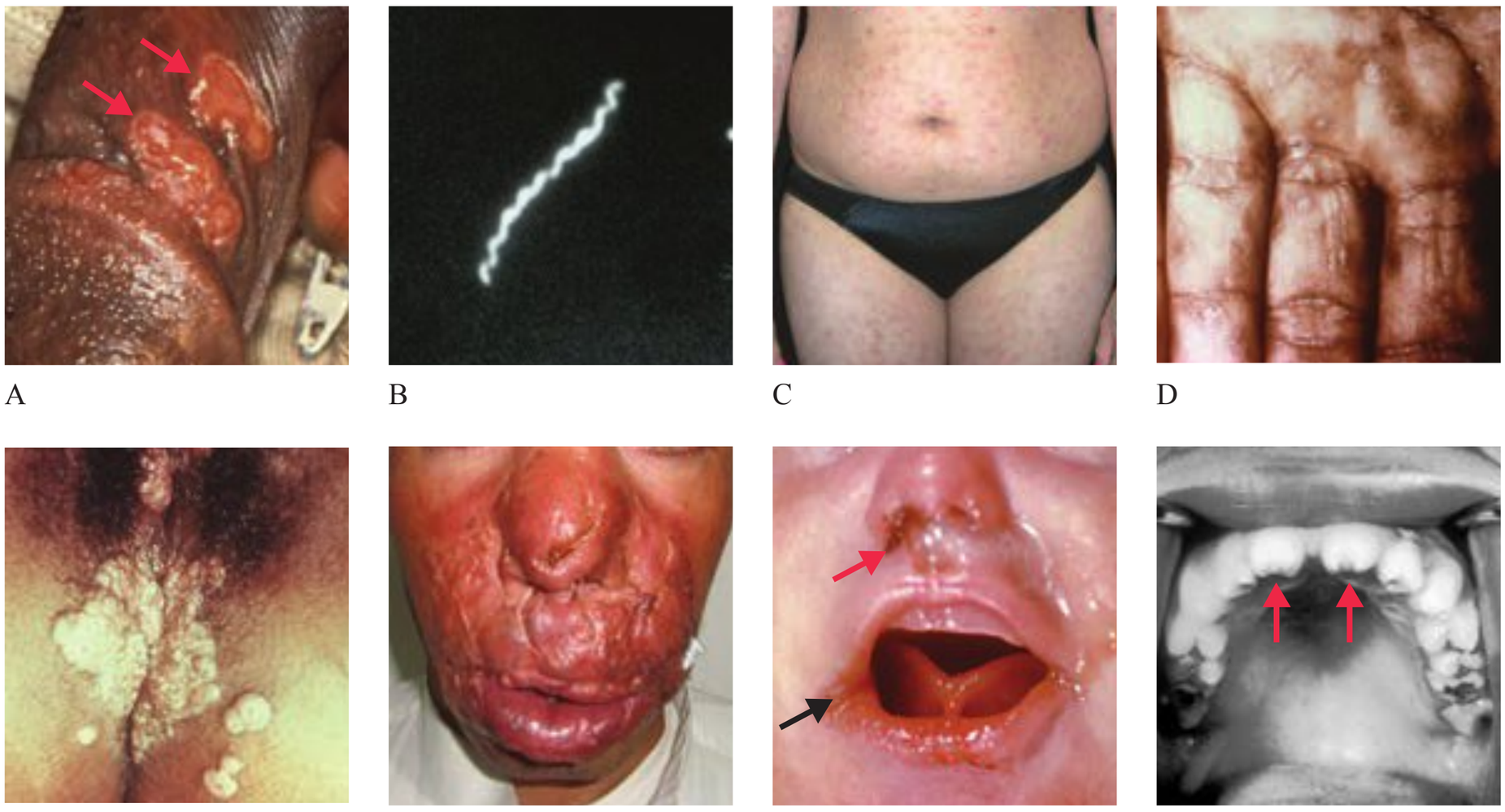


FIGURE 2.8-25. Syphilis. (A) Localized disease presenting with painless chancre and **(B)** dark-field microscopy visualizing treponemes in fluid from chancre in **1° syphilis.** Maculopapular rash **(C)** [including palms and soles **(D)**] and **(E)** condylomata lata in **2° syphilis. (F)** Gummas (chronic granulomas) in **3° syphilis. (G)** Rhagades (linear scars at angle of mouth), snuffles (nasal discharge), saddle nose, and **(H)** notched (Hutchinson) teeth in **congenital syphilis.** (Part A reproduced with permission from the US Department of Health and Human Services and M. Rein. Part B reproduced with permission from the US Department of Health and Human Services and Renelle Woodall. Part C used with permission from Dr. Richard Usatine. Part D reproduced with permission from the US Department of Health and Human Services and Robert Sumpter. Parts E, H reproduced with permission from the US Department of Health and Human Services and Susan Lindsley. Part F adapted with permission from Chakir K, Benchikhi H. Centro-facial granuloma revealing a tertiary syphilis, Pan Afr Med J. 2013 Jun 30;15:82. Part G reproduced with permission from the US Department of Health and Human Services and Dr. Norman Cole.)



FIGURE 2.8-26. Condylomata lata. Typical appearance of the verrucous, heaped-up lesions of condylomata lata. (Reproduced with permission from Tintinalli JE et al. Tintinalli's Emergency Medicine: A Comprehensive Study Guide, 7th ed. New York, NY: McGraw-Hill; 2011.)

KEY FACT

Syphilis is the "great imitator" because its dermatologic findings resemble those of many other diseases.

- **Early latent** (period from resolution of 1° or 2° syphilis to the end of the **first year** of infection): No symptoms; ⊕ serology.
- **Late latent** (period of asymptomatic infection **beyond the first year**): No symptoms; ⊕ or ⊖ serology. One-third of cases progress to 3° syphilis.
- **3°** (late manifestations appearing 1–20 years after initial infection): Presents with destructive, granulomatous **gummas. Neurosyphilis** includes **tabes dorsalis** (posterior column degeneration), meningitis, and **Argyll Robertson pupil** (constricts with accommodation but not reactive to light). **Cardiovascular** findings include dilated aortic root, aortitis, **aortic root aneurysms,** and aortic regurgitation.

Diagnosis

Table 2.8-9 summarizes relevant diagnostic tests.

- **VDRL: False-⊕ results** are seen with **V**iruses (mononucleosis, HSV, HIV, hepatitis), **D**rugs/IV drug use, **R**heumatic fever/**R**heumatoid arthritis, and SLE/**L**eprosy.
- Neurosyphilis should be suspected and ruled out in patients with AIDS, neurologic symptoms, and a ⊕ **rapid plasma reagin (RPR) test.**

Treatment

- **1°/2°: Benzathine penicillin IM** × one dose. Tetracycline or doxycycline × 14 days may be used for patients with penicillin allergies. Pregnant patients who are penicillin allergic and have ⊕ antibody titers must be desensitized and treated with penicillin.

TABLE 2.8-9. Diagnostic Tests for Syphilis

Test	Comments
Dark-field microscopy	Identifies motile spirochetes (only 1° and 2° lesions).
VDRL/RPR	Nontreponemal tests. Rapid and cheap, but sensitivity is only 75–85% in 1° disease. Many false-⊕ results. Used for screening and quantitative measurement.
FTA-ABS, TP-PA, MHA-TP, TP-EIA	Treponemal tests. Sensitive and specific. Used as confirmatory tests.

- **Latent infection:** Treat with benzathine penicillin. Give one dose for early latent infection; give a weekly dose × 3 weeks for late latent infection or for asymptomatic infection of unknown duration.
- **Neurosyphilis:** Treat with penicillin IV × 10–14 days; penicillin-allergic patients should be desensitized prior to therapy.

GENITAL LESIONS

See Table 2.8-10 for a description of common sexually transmitted genital lesions along with an outline of their diagnosis and treatment.

Genitourinary Infections

URINARY TRACT INFECTIONS

Affect women more frequently than men, and ⊕ E coli cultures are obtained in 80% of cases. See the mnemonic **SEEKS PP** for other pathogens. Risk factors include the presence of catheters or other urologic instrumentation, anatomic abnormalities (eg, BPH, vesicoureteral reflux), previous UTIs or pyelonephritis, DM, recent antibiotic use, immunosuppression, and pregnancy.

History/Pe

- Present with **dysuria, urgency, frequency,** suprapubic pain, and hematuria.
- Children may present with **bedwetting,** poor feeding, recurrent fevers, and foul-smelling urine.
- Elderly patients may present with delirium/acute confusion and few other symptoms.
- The differential includes vaginitis, STDs, urethritis or acute urethral syndrome, and prostatitis.

Diagnosis

- Diagnosed by **clinical symptoms.** In the absence of symptoms, treatment is warranted only for children, patients with anatomic GU tract anomalies, pregnant women, those with instrumented urinary tracts, patients scheduled for GU surgery, and renal transplant patients.
- **Urine dipstick/urinalysis (UA): best initial test. ↑ leukocyte esterase** (a marker of WBCs) is 75% sensitive and up to 95% specific. ↑ **nitrites**

KEY FACT

Remember that treatment of syphilis can result in an acute flulike illness (headache, fever, chills, myalgias) known as the **Jarisch-Herxheimer reaction,** which results from the release of endotoxins by the killed organisms.

KEY FACT

Genital lesions caused by Haemophilus "do cry," and herpes lesions are painful. The others are painless.

MNEMONIC

Common UTI bugs—

SEEKS PP

Serratia
Ecoli
Enterobacter
Klebsiella pneumoniae
Staphylococcus saprophyticus
Pseudomonas
Proteus mirabilis

TABLE 2.8-10. Sexually Transmitted Genital Lesions

Variable	Klebsiella granulomatis[a] (granuloma inguinale)	Haemophilus ducreyi (chancroid)	HSV-1 or HSV-2[b]	HPV[c]	Treponema pallidum
Lesion	Papule becomes a **beefy-red ulcer** with a characteristic rolled edge of granulation tissue (see Figure 2.8-27).	Papule or pustule (chancroid; see Figure 2.8-28).	Vesicle (3–7 days postexposure, see Figure 2.8-29).	Papule (condylomata acuminata, see Figure 2.8-30; warts).	Papule (chancre, see Figure 2.8-25A).
Appearance	Raised red lesions with a white border.	Irregular, deep, well demarcated, necrotic.	Regular, red, shallow ulcer.	Irregular, pink or white, raised; cauliflower.	Regular, red, round, raised.
Number	1 or multiple	1–3	Multiple	Multiple	Single
Size	5–10 mm	10–20 mm	1–3 mm	1–5 mm	1 cm
Pain	No	**Yes**	**Yes**	No	No
Concurrent signs and symptoms	Granulomatous ulcers.	Inguinal lymphadenopathy.	Malaise, myalgias, and fever with vulvar burning and pruritus.	Pruritus.	Regional adenopathy.
Diagnosis	Clinical exam, biopsy (Donovan bodies).	Difficult to culture; diagnosis is made on clinical grounds, culture on specialized media.	Tzanck smear shows multinucleated giant cells (best initial test; Figure 2.8-31); viral cultures (most accurate test); DFA or serology.	Clinical exam; biopsy for confirmation.	Spirochetes seen under dark-field microscopy; T pallidum identified by serum antibody test.
Treatment[d]	Doxycycline or azithromycin.	Azithromycin or ceftriaxone.	Acyclovir, famciclovir, or valacyclovir for 1° infection.	Cryotherapy, laser, or excision; topical agents such as podophyllotoxin, imiquimod, or trichloroacetic acid.	Penicillin IM.

[a] Previously known as Calymmatobacterium granulomatis.

[b] Some 85% of genital herpes lesions are caused by HSV-2.

[c] HPV serotypes 6 and 11 are associated with genital warts; types 16, 18, and 31 are associated with cervical cancer.

[d] For all, treat sexual partners.

(a marker of bacteria), ↑ urine pH (Proteus infections), and hematuria (seen with cystitis) are also commonly seen.

- **Microscopic analysis: Pyuria** (> 5 WBCs/hpf) and **bacteriuria** (1 organism/hpf = 10^6 organisms/mL) are suggestive.
- **Urine culture: Most accurate test.** The gold standard is > **10^5 CFU/mL.**

Treatment

- **Uncomplicated UTI:** Treat on an outpatient basis with PO **TMP-SMX** or a **fluoroquinolone** × 3 days, or **nitrofurantoin** × 5 days. The use of fluoroquinolones should be reserved for severe symptoms in light of resistance and MRSA selection.
- **Complicated UTI** (urinary obstruction, UTI in men, renal transplant, catheters, instrumentation): Administer the same antibiotics as above, but for 7–14 days.
- **Pregnant patients:** Treat asymptomatic bacteriuria or symptomatic UTI with **nitrofurantoin,** oral cephalosporin, or amoxicillin × 3–7 days. Avoid fluoroquinolones, TMP-SMX, and tetracyclines. Confirm clearance with a post-treatment urine culture.
- **Urosepsis:** Patients with urosepsis should be hospitalized and initially treated with **IV antibiotics.** Consider broader coverage to include resistant GNRs or enterococcus.
- Prophylactic antibiotics may be given to women with uncomplicated recurrent UTIs. Check for prostatitis in men.

PYELONEPHRITIS

Nearly 85% of community-acquired cases of pyelonephritis result from the same pathogens that cause cystitis. Cystitis and pyelonephritis have similar risk factors.

History/Pe

- Signs and symptoms are similar to those of cystitis but show evidence of **upper urinary tract disease.**
- Symptoms include **flank pain, fever/chills,** and nausea/vomiting. Dysuria, frequency, and urgency are also possible.

Diagnosis

- **UA and culture:** Results are similar to those of cystitis, but with **WBC casts.** Send blood cultures to rule out urosepsis.
- **CBC:** Reveals leukocytosis.
- **Imaging:** In general, imaging is not necessary. Patients who relapse or do not respond to therapy within 48–72 hours should be evaluated by ultrasound or CT for obstruction, abscess, and other complications.

Treatment

- For mild cases, patients may be treated on an outpatient basis for 7–14 days. **Fluoroquinolones** are first-line therapy. Encourage ↑ PO fluids and monitor closely.
- Admit and administer IV antibiotics to patients who have serious medical complications or systemic symptoms, are **pregnant,** present with severe **nausea and vomiting,** or have suspected bacteremia. Fluoroquinolones, third- or fourth-generation cephalosporins, β-lactam/β-lactamase inhibitors, and carbapenem can be used depending on disease severity.



FIGURE 2.8-27. Ulcerogranulomatous penile lesion of donovanosis. (Reproduced with permission from Longo DL et al. Harrison's Principles of Internal Medicine, 18th ed. New York, NY: McGraw-Hill; 2012.)

KEY FACT

Pyelonephritis is the most common serious medical complication of pregnancy. Among patients with untreated bacteriuria, 20–30% will develop pyelonephritis.

KEY FACT

When in doubt, hospitalize a patient with pyelonephritis and administer IV antibiotics.

Hematologic Infections

SEPSIS

Defined as the presence of **systemic inflammatory response syndrome (SIRS)** with a **documented infection** induced by microbial invasion or tox-

KEY FACT

Urosepsis should be considered in any elderly patient with altered mental status.



FIGURE 2.8-28. Chancroid. Multiple, painful ulcers are seen on the labia. (Reproduced with permission from Wolf K, Johnson RA, Saavedra AP. Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology, 7th ed. New York, NY: McGraw-Hill; 2013.)

KEY FACT

SIRS = two or more of the following:

1. **Temperature:** Either < 36°C or > 38°C (ie, hypothermia or fever).
2. **Tachypnea:** > 20 breaths per minute or $Paco_2$ < 32 mm Hg on ABG.
3. **Tachycardia:** Heart rate > 90 bpm.
4. **Leukocytosis/leukopenia:** WBC count < 4000 cells/mm^3 or > 12,000 cells/mm^3 or > 10% immature (band) forms.



FIGURE 2.8-29. Genital herpes caused by HPV-2. Note group of vesicles on shaft of penis. (Reproduced with permission from Wolf K, Johnson R, Saavedra A. Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology, 7th ed. New York, NY: McGraw-Hill; 2013.)

ins in the bloodstream. **Severe sepsis** refers to sepsis with end-organ dysfunction due to poor perfusion. **Septic shock** refers to sepsis with hypotension and organ dysfunction from vasodilation. Examples include the following:

- **Gram-⊕ shock** (eg, staphylococci and streptococci) 2° to fluid loss caused by exotoxins.
- **Gram-⊖ shock** (eg, E coli, Klebsiella, Proteus, and Pseudomonas) 2° to vasodilation caused by endotoxins (lipopolysaccharide).
- **Neonates:** GBS, E coli, Listeria monocytogenes, H in*fl*uenzae.
- **Children:** H in*fl*uenzae, pneumococcus, meningococcus.
- **Adults:** Gram-⊕ cocci, aerobic gram-⊖ bacilli, anaerobes (dependent on the presumed site of infection).
- **IV drug users/indwelling lines:** S aureus, coagulase-⊖ Staphylococcus species.
- **Asplenic patients:** Pneumococcus, H in*fl*uenzae, meningococcus (encapsulated organisms).

History/Pe

- Presents with abrupt onset of fever and chills, altered mental status, tachycardia, and tachypnea. Severe sepsis may lead to end-organ dysfunction such as renal or hepatic failure. **Hypotension** occurs in cases of septic shock.
- **Septic shock** is typically a warm shock with **warm skin and extremities.** This contrasts with cardiogenic shock, which typically presents with **cool skin and extremities.**
- Petechiae, ecchymoses, or abnormal coagulation tests suggest DIC (2–3% of cases).

Diagnosis

- A clinical diagnosis.
- Labs show leukocytosis or leukopenia with ↑ bands, thrombocytopenia (50% of cases), evidence of ↓ tissue perfusion (↑ creatinine, ↑ LFTs, ↑ lactate), and abnormal coagulation studies (↑ INR).
- It is critical to obtain cultures of all appropriate sites (eg, blood, sputum, CSF, wound, urine).
- Imaging (CXR, CT) may aid in establishing the etiology or site of infection.

Treatment

- ICU admission may be required. Treat aggressively with **IV fluids, empiric antibiotics** (based on the likely source of infection), and **vasopressors.**
- Treat underlying factors (eg, remove Foley catheter or infected lines).
- The 1° goal is to **maintain BP** and **perfuse** end organs.

MALARIA

A protozoal disease caused by four species of the genus Plasmodium (P falciparum, P vivax, P ovale, P malariae) and transmitted by the bite of an infected female Anopheles mosquito. P falciparum **has the highest morbidity and mortality,** occasionally within 24 hours of symptom onset. Travelers to endemic areas should take chemoprophylaxis and use mosquito repellent and bed nets to minimize exposure.

History/Pe

- Patients have a history of exposure in a malaria-endemic area, with **periodic** attacks of sequential **chills, fever (> 41°C, or > 105.8°F),** and **diaphoresis** occurring over 4–6 hours.
- **Splenomegaly** often appears 4 or more days after symptom onset. Patients are often asymptomatic between attacks, which recur every 2–3 days depending on the Plasmodium species involved.
- Severely ill patients may present with hyperpyrexia, prostration, impaired consciousness, agitation, hyperventilation, and bleeding. The presence of rash, skin ulcer, eosinophilia, lymphadenopathy, neck stiffness, or photophobia suggests a different or additional diagnosis.

Diagnosis

- Timely diagnosis of the correct species is essential, because P falciparum can be fatal and is often resistant to standard chloroquine treatment.
- **Giemsa- or Wright-stained thick and thin blood films** should be sent for expert microscopic evaluation to determine the species as well as the degree of parasitemia (see Figure 2.8-32).
- CBC usually demonstrates normochromic, normocytic anemia with reticulocytosis.
- If resources allow, more sensitive serologic tests are available, including rapid antigen detection methods, fluorescent antibody methods, and PCR.

Treatment

- Uncomplicated malarial infection can be treated orally. **Chloroquine** has been the standard antimalarial medication, but increasing resistance often necessitates the use of other medications.
- In cases of P vivax, P ovale, or an unknown species, **primaquine** is added to eradicate the hypnozoites in the liver.
- Severe infections can be treated with parenteral antimalarial medications **(IV quinidine)** with transition to oral regimens as tolerated. Symptoms can be treated with supportive care.
- **Atovaquone-proguanil and mefloquine are possible first-line chemoprophylaxis agents against chloroquine-resistant malaria.**

Complications

Cerebral malaria, severe hemolytic anemia, renal impairment, noncardiogenic pulmonary edema, hypoglycemia, lactic acidosis, acute hepatopathy, gram-⊖ bacteremia.

INFECTIOUS MONONUCLEOSIS

Most commonly occurs in **young adult** patients; usually due to acute EBV infection. Transmission most often occurs through exchange of body fluids, most commonly saliva.

History/Pe

- Presents with **fever** and **pharyngitis** (see Figure 2.8-33). **Fatigue** invariably accompanies initial illness and may persist for 3–6 months. Examination may reveal **low-grade fever, generalized lymphadenopathy** (especially **posterior cervical**), tonsillar exudate and enlargement, palatal petechiae, a generalized maculopapular rash, **splenomegaly,** and **bilateral upper eyelid edema. Symptoms appear 2–5 weeks after infection.**
- Patients who present with pharyngitis as their 1° symptom may be mis-



FIGURE 2.8-30. Condylomata acuminata. (Used with permission of Dr. Wiesner, Public Health Image Library, Centers for Disease Control and Prevention, Atlanta, GA.)

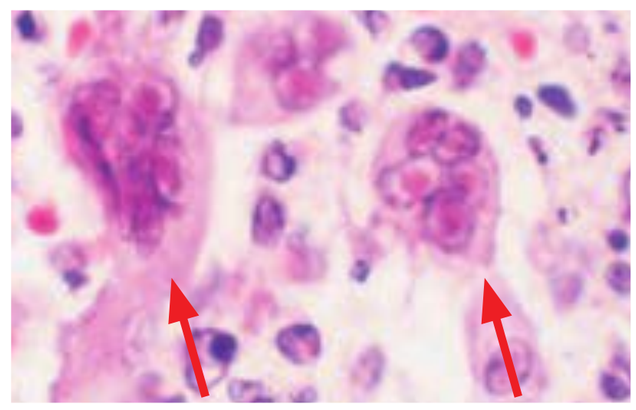


FIGURE 2.8-31. ⊕ Tzank smear in genital herpes (HSV-2) with multinucleated giant cells. (Used with permission from Yale Rosen.)

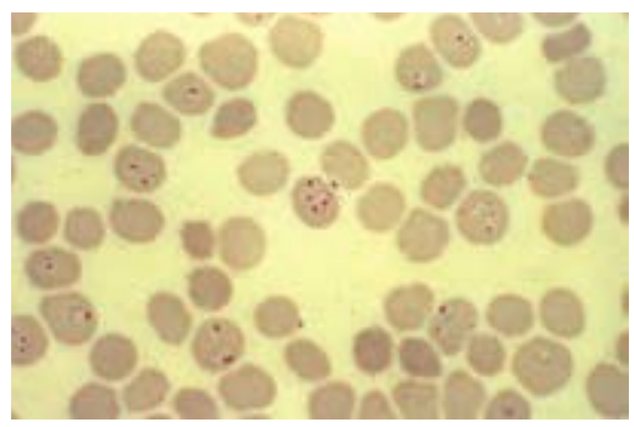


FIGURE 2.8-32. Plasmodium falciparum hyperparasitemia in the thin smear of a patient with cerebral malaria. (Used with permission of Dr. S. Glenn, Public Health Image Library, Centers for Disease Control and Prevention, Atlanta, GA.)

KEY FACT

Consider malaria in the differential diagnosis for any patient who has emigrated from or recently traveled to tropical locations and presents with fever.

KEY FACT

P vivax, P ovale, and P malariae can all cause symptoms months to years after the initial infection.



FIGURE 2.8-33. **Pharyngitis.** (Used with permission from Dr. Richard Usatine.)

diagnosed with streptococcal pharyngitis (30% of patients with infectious mononucleosis are asymptomatic carriers of GAS in their oropharynx).
- The differential diagnosis also includes **CMV,** toxoplasmosis, HIV, HHV-6, other causes of viral hepatitis, and lymphoma.

Diagnosis

- Diagnosed by the **heterophil antibody (Monospot) test** (may be ⊖ in the first few weeks after symptoms begin).
- **EBV-specific antibodies** can be ordered in patients with suspected mononucleosis and a ⊖ Monospot test. **Infectious mononucleosis syndromes that are Monospot ⊖ and EBV-antibody ⊖ are most often due to CMV infection.** Acute HIV and other viral etiologies should be considered.
- CBC with differential often reveals mild **thrombocytopenia** with relative **lymphocytosis** and > 10% **atypical T lymphocytes.**
- Comprehensive metabolic panel usually reveals mildly elevated transaminases, alkaline phosphatase, and total bilirubin.

Treatment

Treatment is mostly supportive, as there is no effective antiviral therapy. Corticosteroids are indicated for airway compromise due to tonsillar enlargement, severe thrombocytopenia, or severe autoimmune hemolytic anemia.

Complications

- **CNS infection:** Can present as aseptic meningitis, encephalitis, meningoencephalitis, cranial nerve palsies (particularly CN VII), optic and peripheral neuritis, transverse myelitis, or Guillain-Barré syndrome.
- **Splenic rupture:** Occurs in < 0.5% of cases. More common in men, and presents with abdominal pain, referred left shoulder pain, or hemodynamic compromise. Patients should avoid contact sports for at least 4 weeks to prevent this complication.
- **Upper airway obstruction:** Treat with steroids.
- **Bacterial superinfection:** Many patients develop a 2° streptococcal pharyngitis.
- **Fulminant hepatic necrosis:** More common in men; the most common cause of death in affected men.
- **Autoimmune hemolytic anemia:** Occurs in 2% of patients during the first

KEY FACT

Obtain a fingerstick in a patient with malaria and mental status changes to rule out hypoglycemia.

KEY FACT

Nearly all malaria-endemic countries now have chloroquine-resistant malaria.

KEY FACT

Cerebral malaria presents with headache, a change in mental status, neurologic signs, retinal hemorrhages, convulsions, and delirium. If left untreated, it can rapidly progress to coma and death.

KEY FACT

A young adult who presents with the triad of **fever, sore throat,** and **lymphadenopathy** may have infectious mononucleosis.

KEY FACT

The lymphocytosis in EBV infection is predominantly due to B-cell proliferation, but the atypical cells are T lymphocytes.

KEY FACT

Most patients with mononucleosis who are given ampicillin for suspected streptococcal pharyngitis develop a prolonged, pruritic maculopapular rash.

2 weeks. Coombs ⊕. Mild anemia lasts 1–2 months. Treat with corticosteroids if severe.

Fever

FEVER OF UNKNOWN ORIGIN

A temperature of > 38.3°C (> 100.9°F) of at least 3 weeks' duration that remains undiagnosed following 3 outpatient visits or 3 days of hospitalization.

History/Pe

Presents with fever, headache, myalgia, and malaise. The differential diagnosis includes the following:

- **Infectious:** TB, endocarditis (eg, HACEK organisms; see the discussion of infective endocarditis), occult abscess (abdominal, prostatic), osteomyelitis, catheter infections, sinusitis. In HIV patients, consider MAC, histoplasmosis, or CMV.
- **Neoplastic:** Lymphomas, leukemias, hepatic and renal cell carcinomas.
- **Autoimmune:** Still disease, SLE, cryoglobulinemia, polyarteritis nodosa, connective tissue disease, granulomatous disease (including sarcoidosis).
- **Miscellaneous:** Pulmonary emboli/DVT, IBD, alcoholic hepatitis, drug fever, familial Mediterranean fever, factitious fever.
- **Idiopathic** (10–15%).

Diagnosis

- Confirm the presence of fever, and take a detailed history, including family, social, sexual, occupational, dietary, exposures (pets/animals), and travel.
- **Labs:** Obtain a CBC with differential, ESR, serum protein electrophoresis, multiple blood cultures, sputum Gram stain and culture, UA and culture, and PPD. Specific tests (ANA, RF, CK, viral cultures, viral serologies/antigen tests) can be obtained if an infectious or autoimmune etiology is suspected.
- **Imaging:** Obtain a CXR. CT of the chest, abdomen, and pelvis should be done early in the workup of a true FUO. Invasive testing (marrow/liver biopsy) is generally low yield. Laparoscopy and colonoscopy are higher yield as second-line tests (after CT).

Treatment

Stop unnecessary medications. Patients with FUO and a completely ⊖ workup have a good prognosis, with fevers resolving over months to years.

NEUTROPENIC FEVER

- Defined as a single oral temperature of ≥ 38.3°C (≥ 101°F) or a temperature of ≥ 38°C (≥ 100.4°F) for ≥ 1 hour in a neutropenic patient (ie, an absolute neutrophil count < 500 cells/mm^3).
- **Hx/PE:** Common in cancer patients undergoing chemotherapy (neutropenic nadir 7–10 days postchemotherapy). Inflammation may be minimal or absent.
- **Dx:**
  - Conduct a thorough physical examination, but **avoid a rectal examination** in light of the bleeding risk if the patient is thrombocytopenic.

KEY FACT

Overall, infections and cancer account for the majority of cases of FUO (> 60%). Autoimmune diseases account for □15%. In the elderly, rheumatic diseases account for one-third of cases.

KEY FACT

FUO patients without other symptoms do not require empiric antibiotic therapy.

Q 1

A 45-year-old woman presents to the ED with fever, chills, nausea, vomiting, and severe flank pain. She has a history of multiple UTIs and was recently hospitalized for pyelonephritis. UA reveals pyuria and bacteriuria. Ultrasound performed in the ED shows what appears to be a perinephric abscess. What is the next most appropriate step in management?

Q 2

A 17-year-old boy presents with 1 week of fever, sore throat, and progressive fatigue. PE reveals palatal petechiae, large tonsils with whitish exudates, splenomegaly, and cervical and axillary lymphadenopathy. The patient says that he has been too tired to attend football practices and is concerned that he may lose his spot on the starting roster. What is the most appropriate advice to be given regarding his participation in athletics?

- Obtain a CBC with differential, serum creatinine, BUN, and transaminases; send blood, urine, lesion, sputum, and stool cultures. Consider testing for viruses, fungi, and mycobacteria.
- CXR for patients with respiratory symptoms; CT scan to evaluate for abscesses or other occult infection.

- **Tx:** Empiric antibiotic therapy with anti-pseudomonal agent (cefepime, piperacillin-tazobactam). Admission and IV antibiotics are warranted for high-risk patients (eg, hematologic malignancy, chemotherapy, neutropenia > 14 days). Routine use of colony-stimulating factors is not indicated. **If fevers persist after 72 hours despite antibiotic therapy, start antifungal treatment.**

KEY FACT

Ehrlichiosis is a disease transmitted by the lone star tick endemic to the south central and southeastern parts of the United States. It leads to headache, fever, chills, altered mental status, and myalgias, but rash is uncommon. Leukopenia, thrombocytopenia, and ↑ liver enzymes are common laboratory findings. Doxycycline is the treatment of choice.

Tick-Borne Infections

LYME DISEASE

- A tick-borne disease caused by the spirochete Borrelia burgdorferi. Usually seen during the **summer months,** and carried by Ixodes ticks on white-tailed deer and white-footed mice. Endemic to the **Northeast,** northern Midwest, and Pacific coast.
- **Hx/PE:** Presents with the onset of rash with fever, malaise, fatigue, headache, myalgias, and/or arthralgias. Infection usually occurs after a tick feeds for > 18 hours.
  - **1° (early localized disease): Erythema migrans** begins as a small erythematous macule or papule that is found at the tick-feeding site and expands slowly over days to weeks. The border may be macular or raised, often with central clearing ("bull's eye"; see Figure 2.8-34).
  - **2° (early disseminated disease):** Presents with migratory polyarthropathies, neurologic phenomena (eg, Bell palsy [bilateral Bell palsy is clas-



FIGURE 2.8-34. Erythema chronicum migrans seen in Lyme disease. Note the classic "bull's eye" lesion, which consists of an outer ring where the spirochetes are found, an inner ring of clearing, and central erythema due to an allergic response at the site of the tick bite.
(Used with permission of James Gathany, Public Health Image Library, Centers for Disease Control and Prevention, Atlanta, GA, as published in McPhee SJ et al. Current Medical Diagnosis & Treatment 2010. New York, NY: McGraw-Hill; 2010.)

1 A

Hospitalize the patient for empiric broad-spectrum antibiotics.
This patient has complicated pyelonephritis and therefore needs to be initially managed as an inpatient. Antibiotic therapy can subsequently be narrowed and converted to PO as patient circumstances permit.

2 A

Tell the patient to refrain from contact sports until his physical examination normalizes. Splenomegaly 2° to infectious mononucleosis puts him at ↑ risk for splenic rupture.

sical for Lyme disease]), meningitis and/or myocarditis, and conduction abnormalities (third-degree heart block).
  - **3° (late disease):** Arthritis and subacute encephalitis (memory loss and mood change).
- **Dx:**
  - Early Lyme disease is diagnosed on clinical grounds alone (erythema migrans + endemic area). Serologic tests are not required or recommended, as IgM becomes ⊕ 1–2 weeks, and IgG 2–6 weeks after onset of erythema migrans.
  - Early disseminated and late Lyme disease are diagnosed based on clinical syndrome (multiple erythema migrans lesions, lymphocytic meningitis, facial palsy, radiculoneuropathy, carditis, heart block) + endemic area + positive serologies (IgM and IgG antibodies to B burgdorferi).
  - Indications for serologic testing (must meet all criteria): endemic area + exposure risk factor + symptoms consistent with early disseminated or late disease. Order ELISA IgM and IgG, if positive or equivocal, then Western blot for confirmation. Do not use for "screening" or nonspecific symptoms. Western blots sent without ELISA have high false-⊕ rates.
    - **Tissue culture/PCR:** Extremely difficult to obtain; not routinely done.
- **Tx:**
  - Treat early disease with **doxycycline** (or amoxicillin in children < 8 years of age and in pregnant patients); more advanced disease (eg, CNS or arthritic disease) should be treated with **ceftriaxone.**
  - Consider empiric therapy for patients with the characteristic rash, arthralgias, or a tick bite acquired in an endemic area. Prevent with tick bite avoidance.
  - **Prophylaxis:** Lyme disease is not usually transmitted within the first 48 to 72 hours of tick attachment. Give one dose of doxycycline if all the following apply: tick is Ixodes scapularis and has been attached for > 36 hours, prophylaxis is begun within 72 hours of removal, local rate of infection of ticks with B burgdorferi is > 20%, and doxycycline is not contraindicated. If criteria not met, observe and only treat if erythema migrans develops.

ROCKY MOUNTAIN SPOTTED FEVER

- A disease caused by Rickettsia rickettsii and carried by the American dog tick (Dermacentor variabilis). The organism invades the endothelial lining of capillaries and causes **small vessel vasculitis.**
- **Hx/PE:** Presents with **headache, fever,** malaise, and **rash.** The characteristic rash is initially macular (beginning on the wrists and ankles) but becomes petechial/purpuric as it spreads centrally (see Figure 2.8-35). Altered mental status or DIC may develop in severe cases.
- **Dx:** Clinical diagnosis should be confirmed with biopsy and indirect immunofluorescence of the skin lesion.
- **Tx: Doxycycline** or chloramphenicol (for pregnant women). The condition can be rapidly fatal if left untreated. If clinical suspicion is high, begin treatment while awaiting testing. Prevent by avoiding tick bites.

KEY FACT

"Tick testing" is a common incorrect answer choice; it has no effect on management and is not performed in a Lyme workup.

KEY FACT

Lyme disease is the most common vector-borne disease in North America.

KEY FACT

Lyme arthritis can be very subtle and minimally inflammatory, and it can wax and wane.

KEY FACT

Rocky Mountain spotted fever starts on the wrists and ankles and then spreads centrally.

Q

A 70-year-old woman with a history of hypertension and lymphoma presents with nausea, vomiting, and fever for the past 2 days. She just underwent her second cycle of high-dose chemotherapy. She has a temperature of 38.5°C (101.3°F). Her CXR is unchanged, and her WBC count is 900 with 25% neutrophils. After urine and blood cultures have been sent, what is the next step in management?



FIGURE 2.8-35. Rocky Mountain spotted fever. These erythematous macular lesions will evolve into a petechial rash that will spread centrally. (Reproduced with permission from Wolf K, Johnson RA, Saavedra AP. Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology, 7th ed. New York, NY: McGraw-Hill; 2013.)

MNEMONIC

Important PE findings of vision-threatening conditions. Abnormalities in the following (4 P's)—

Pupils
Pressure (intraocular)
Picture (vision)
Proptosis

KEY FACT

Orbital cellulitis can be distinguished from preseptal cellulitis by the following clinical features: **restricted eye movements, ↓ visual acuity, diplopia, and proptosis.**

KEY FACT

Neisseria conjunctivitis is an ocular emergency often requiring inpatient parenteral antibiotic therapy.

A

Admit the patient and begin IV antibiotics with an antipseudomonal β-lactam (eg, cefepime, piperacillin-tazobactam, meropenem, imipenem). Febrile, neutropenic patients who are on high-dose chemotherapy have a hematologic malignancy, or have been neutropenic for > 14 days should be admitted for empiric IV antibiotics.

Infections of the Eyes and Ears

INFECTIOUS CONJUNCTIVITIS

A common complaint in the ED setting, inflammation of the conjunctiva is most often bacterial or viral but can also be fungal, parasitic, allergic, or chemical. It is essential to differentiate potentially vision-threatening infectious etiologies from allergic or other causes of conjunctivitis, as well as to identify other vision-threatening conditions that may mimic conjunctivitis. Table 2.8-11 lists the common etiologies of infectious conjunctivitis.

ORBITAL CELLULITIS

- Commonly due to direct spread of infection of the **paranasal sinuses;** can lead to endophthalmitis and blindness. Usually caused by **streptococci, staphylococci (including MRSA), and** H *influenzae* (in children). In diabetic and immunocompromised patients, the Zygomycetes Mucor and Rhizopus must be included in the differential diagnosis.
- **Hx/PE:** Presents with **acute-onset fever, proptosis, ↓ extraocular movement,** ocular pain, and ↓ visual acuity. Look for a **history of ocular trauma/surgery or sinusitis.** Palatal or nasal mucosal ulceration with coexisting maxillary and/or ethmoid sinusitis suggests mucormycosis or Rhizopus.
- **Dx: Mostly clinical.** Blood and tissue fluid culture; CT scan (to rule out orbital abscess and intracranial involvement).
- **Tx:**
  - **Admit and give immediate IV antibiotics;** request an **ophthalmologic/ENT** consult.
  - Abscess formation or a worsening condition may necessitate surgery.
  - **Diabetic and immunocompromised patients** should be treated with **amphotericin B and surgical debridement** (often associated with **cavernous sinus thrombosis**) if Mucor or Rhizopus is diagnosed.

TABLE 2.8-11. Common Causes of Infectious Conjunctivitis

pathogen	characteriStics	diagnoSiS	treatMent
		bacterial	
Staphylococci, streptococci, Haemophilus, Pseudomonas, Moraxella	Foreign body sensation, purulent discharge.	Gram stain and culture if severe.	Antibiotic drops/ointment.
Ngonorrhoeae	**An emergency!** Corneal involvement can lead to perforation and blindness.	Gram stain shows gram-⊖ intracellular diplococci.	IM or IV ceftriaxone. **Inpatient** treatment if complicated.
Ctrachomatis A–C	**Neonatal infection: mucopurulent conjunctivitis. Trachoma (global): recurrent epithelial keratitis** in childhood; trichiasis, corneal scarring, and entropion. **The leading cause of preventable blindness worldwide.**	Neonatal infection: Giemsa stain, chlamydial cultures. Trachoma: clinical (most often), PCR.	Neonatal: Azithromycin, tetracycline, or erythromycin × 3–4 weeks in infants. Trachoma: (single oral dose) in mass treatment. Surgery if needed to protect cornea from eyelashes.
		Viral	
Adenovirus (most common)	Copious **watery discharge,** severe ocular irritation, preauricular lymphadenopathy. Occurs in epidemics.		**Contagious;** self-limited. Topical corticosteroids with supervision by an ophthalmologist.

OTITIS EXTERNA

- An inflammation of the external auditory canal, also known as "swimmer's ear." Pseudomonas and Enterobacteriaceae are the most common etiologic agents. Both grow in the presence of excess moisture.
- **Hx/PE:** Presents with pain, pruritus, and possible purulent discharge. Examination reveals **pain with movement of the tragus/pinna** (unlike otitis media) and an edematous and erythematous ear canal. See the Pediatrics chapter for a discussion of otitis media.
- **Dx:** A clinical diagnosis. Obtain a culture for severe or refractory cases. Order a CT scan if the patient appears toxic.
- **Tx: Clean the ear** and give **antibiotic** (ofloxacin or ciprofloxacin) and steroid eardrops. Add systemic antibiotics in patients with severe disease, immunodeficiency, or diabetes. Elderly diabetics and immunocompromised individuals are at risk for necrotizing otitis externa and may require IV antibiotics (usually a fluoroquinolone or third-/fourth-generation cephalosporin + aminoglycoside).

KEY FACT

Diabetics are at risk for malignant otitis externa.

Miscellaneous Infections

INFECTIVE ENDOCARDITIS

Infection of the endocardium. Most commonly affects the heart valves, especially the mitral valve. Risk factors include rheumatic, congenital, or valvular heart disease; prosthetic heart valves; IV drug abuse; and immunosuppression. Etiologies are as follows (see also Table 2.8-12):

- S aureus: The causative agent in > 80% of cases of acute bacterial endocarditis in patients with a history of **IV drug abuse.**
- Viridans **streptococci:** The most common pathogens for left-sided subacute bacterial endocarditis and following **dental procedures in native valves.**
- **Coagulase-⊖** Staphylococcus: The most common infecting organism in **prosthetic valve** endocarditis.
- Streptococcus bovis: S bovis endocarditis is associated with coexisting **GI malignancy.** Perform colonoscopy if S bovis diagnosed.
- Candida **and** Aspergillus **species:** Account for most cases of fungal endocarditis. Predisposing factors include long-term indwelling IV catheters, malignancy, AIDS, organ transplantation, and IV drug use.

KEY FACT

Otitis media should not cause pain with movement of the tragus/pinna.

MNEMONIC

Presentation of endocarditis—

FROM JANE

Fever
Roth spots
Osler nodes
Murmur
Janeway lesions
Anemia
Nail hemorrhage
Emboli

HISTORY/PE

- **Constitutional symptoms are common (fever/FUO, weight loss, fatigue).**
- Examination reveals a **heart murmur.** The mitral valve (mitral regurgitation) is more commonly affected than the aortic valve in non–IV drug users; more right-sided involvement is found in IV drug users (tricuspid valve > mitral valve > aortic valve).
- **Osler nodes** (small, tender nodules on the finger and toe pads), **Janeway lesions** (small peripheral hemorrhages; see Figure 2.8-36A), **splinter hemorrhages** (subungual petechiae; see Figure 2.8-36B), **Roth spots** (retinal hemorrhages), focal neurologic deficits from embolic stroke, and other embolic phenomena are also seen.

TABLE 2.8-12. Causes of Endocarditis

Acute	**Subacute**	**Marantic**	**Culture-⊖ (includes HACEK)**	**SLE**
S aureus (IV drug abuse, prosthetic valves) S pneumoniae N gonorrhoeae	Viridans streptococci (native valve, dental procedures) Enterococcus (UTIs) S epidermidis (prosthetic valve) S bovis (GI insult) Fungi	Cancer (poor prognosis). Metastases seed valves; emboli can cause cerebral infarcts.	Haemophilus parainfluenza Actinobacillus Cardiobacterium Eikenella Kingella Coxiella burnetii Brucella Bartonella	Libman-Sacks endocarditis (autoantibody to valve).



A



B

FIGURE 2.8-36. Cutaneous manifestations of infective endocarditis. (A) Janeway lesions. Peripheral embolization to the sole leads to a cluster of erythematous macules known as Janeway lesions. **(B) Splinter hemorrhages.** The splinter hemorrhages shown along the distal aspect of the nail plate are due to emboli from subacute bacterial endocarditis. (Part A reproduced with permission of the Armed Forces Institute of Pathology, Bethesda, MD, as published in Knoop KJ et al. Atlas of Emergency Medicine, 2nd ed. New York, NY: McGraw-Hill; 2002. Part B used with permission of the Department of Dermatology, Wilford Hall USAF Medical Center and Brooke Army Medical Center, San Antonio, TX, as published in Knoop KJ et al. Atlas of Emergency Medicine, 2nd ed. New York, NY: McGraw-Hill; 2002.)

Diagnosis

- Guided by risk factors, clinical symptoms, and the **Duke criteria** (see Table 2.8-13). The presence of two major, one major + three minor, or five minor criteria all merit the diagnosis of endocarditis. Obtain serial blood cultures from different sites before starting antibiotic therapy.
- **CBC** with leukocytosis and left shift; ↑ **ESR** and CRP.

Treatment

- **Early empiric IV antibiotic treatment** for acutely ill patients. Vancomycin + gentamicin is an appropriate choice for most patients. Tailor antibi-

TABLE 2.8-13. Duke Criteria for the Diagnosis of Endocarditis

Criteria	Components
Major	At least two separate ⊕ blood cultures for a typical organism, persistent bacteremia with any organism, or a single ⊕ culture of C burnetii. Evidence of endocardial involvement (via transesophageal echocardiography or new murmur).
Minor	Predisposing risk factors. Fever ≥ 38.3°C (≥ 100.9°F). **Vascular phenomena:** Septic emboli, septic infarcts, mycotic aneurysm, Janeway lesions. **Immunologic phenomena:** Glomerulonephritis, Osler nodes, Roth spots. Microbiologic evidence that does not meet major criteria.

Q

A 41-year-old woman returns to the ED a week after she was discharged for diabetic ketoacidosis treatment. Today she complains of low-grade fever, tenderness and swelling over her face, and a persistent nasal discharge with occasional blood. Physical examination demonstrates necrosis in the left nasal turbinates and left eye proptosis. Specimens from the sinuses show broad, nonseptate hyphae. What is the next most appropriate step in management?

otics once the causative agent is known. Acute valve replacement is sometimes necessary. The prognosis for prosthetic valve endocarditis is poor.

- **Pre-procedure prophylaxis:** Endocarditis prophylaxis is only indicated in patients with:
  - Significant cardiac defects (prosthetic valves, unrepaired cyanotic congenital heart disease, prior history of endocarditis, transplanted heart with valvular disease), and
  - Undergoing high-risk procedures (dental work involving gingival tissue or perforation of mucosa, respiratory tract surgery involving perforation of mucosa, GI or GU surgeries in patients with ongoing GI or GU infections).
- The **preferred antibiotic prophylaxis** is amoxicillin. For patients who are penicillin allergic, use cephalexin, clindamycin, azithromycin, or clarithromycin.

ANTHRAX

Caused by the spore-forming gram-⊕ bacterium Bacillus anthracis. Infection is an occupational hazard for veterinarians, farmers, and individuals who handle **animal wool, hair, hides, or bone meal products.** Also a biologic weapon. B anthracis can cause cutaneous (most common), inhalation (most deadly), or GI anthrax. **There is no person-to-person spread of anthrax.**

History/Pe

- **Cutaneous:** Presents 1–7 days after skin exposure and penetration of spores. The lesion begins as a **pruritic papule** that enlarges to form an ulcer surrounded by a satellite bulbus/lesion with an edematous halo and a round, regular, raised edge. **Regional lymphadenopathy** is also characteristic. The lesion evolves into a **black eschar** within 7–10 days (see Figure 2.8-37).
- **Inhalational:** Presents with fever, dyspnea, hypoxia, hypotension, or symptoms of pneumonia (1–3 days after exposure), classically due to **hemorrhagic mediastinitis.** Patients typically do not have pulmonary infiltrates.
- **GI:** Occurs after the ingestion of poorly cooked, contaminated meat; can present with dysphagia, nausea/vomiting, bloody diarrhea, and abdominal pain.



FIGURE 2.8-37. Cutaneous anthrax. Black eschar is seen on the forearm. (Used with permission of Dr. James H. Steele, Public Health Image Library, Centers for Disease Control and Prevention, Atlanta, GA, as published in Levinson W. Review of Medical Microbiology and Immunology, 11th ed. New York, NY: McGraw-Hill; 2010.)

Diagnosis

Criteria for diagnosis include culture isolation or two nonculture supportive tests (PCR, immunohistochemical staining, or ELISA). CXR is the most sensitive test for inhalational disease (shows a **widened mediastinum** and pleural effusions).



Surgical debridement and amphotericin B. The patient has mucormycosis, a dangerous and aggressive infection found in diabetic and immunocompromised patients. Aggressive surgical debridement is warranted.

Treatment

- **Ciprofloxacin** or doxycycline plus one to two additional antibiotics for at least 14 days are first-line therapy for inhalational disease or cutaneous disease of the face, head, or neck.
- For other cutaneous disease, treat for 7–10 days. Postexposure prophylaxis **(ciprofloxacin)** to prevent inhalation anthrax should be continued for 60 days.

OSTEOMYELITIS

Bone or bone marrow infection 2° to **direct spread** from a soft tissue infection (80% of cases) is most common in adults, whereas infection due to **hematogenous seeding** (20% of cases) is more common in children (metaphyses of the long bones) and IV drug users **(vertebral bodies).** Common pathogens are outlined in Table 2.8-14.

History/Pe

Presents with **localized bone pain and tenderness** along with warmth, swelling, erythema, and limited motion of the adjacent joint. Systemic symptoms (fevers, chills) and purulent drainage may be present.

Diagnosis

- **Labs:** ↑ WBC count; ↑ **ESR** and **CRP** levels in most cases. Blood cultures may be ⊕.
- **Imaging:**
  - X-rays are often ⊖ initially but may show **periosteal elevation** within 10–14 days. Bone scans are sensitive for osteomyelitis but lack specificity.
  - **MRI** (the test of choice) will show ↑ signal in the bone marrow and associated soft tissue infection (see Figure 2.8-38).
  - Definitive diagnosis is made by **bone aspiration** with Gram stain and culture. **Clinical diagnosis made by probing through the soft tissue to bone is usually sufficient,** as aspiration carries a risk of infection.

Treatment

- **Surgical debridement** of necrotic, infected bone followed by **IV antibiotics** × 4–6 weeks. Empiric antibiotic selection is based on the suspected organism and Gram stain.
- Consider clindamycin plus ciprofloxacin, ampicillin/sulbactam, or oxacillin/nafcillin (for methicillin-sensitive S aureus); vancomycin (for MRSA); or ceftriaxone or ciprofloxacin (for gram-⊖ bacteria).

TABLE 2.8-14. Common Pathogens in Osteomyelitis

If	Think
No risk factors	Saureus.
IV drug user	Saureus or Pseudomonas.
Sickle cell disease	Salmonella.
Hip replacement	Sepidermidis.
Foot puncture wound	Pseudomonas.
Chronic	Saureus, Pseudomonas, Enterobacteriaceae.
Diabetic	Polymicrobial, Pseudomonas, Saureus, streptococci, anaerobes.

KEY FACT

Osteomyelitis is associated with peripheral vascular disease, diabetes, penetrating soft tissue injuries, chronic decubitus ulcers, and IV drug abuse.

KEY FACT

Diabetic osteomyelitis should be treated with antibiotics targeting gram-⊕ organisms and anaerobes.

KEY FACT

Penicillin and cephalosporins have minimal cross-reactivity. If a patient had an allergic rash to penicillin, cephalosporins are considered safe. If a patient had an anaphylactic reaction to penicillin, use a non–β-lactam antibiotic.

Q

An 11-year-old black boy with a history of multiple hospitalizations for pain crises, all related to his sickle cell anemia, presents with fever and severe pain in his right hand. Examination shows an area of redness, tenderness, and swelling near the right second metacarpal. Labs show leukocytosis and an elevated ESR. MRI shows an area of ↑ intensity in the painful area. What pathogen is the most likely cause of his condition?

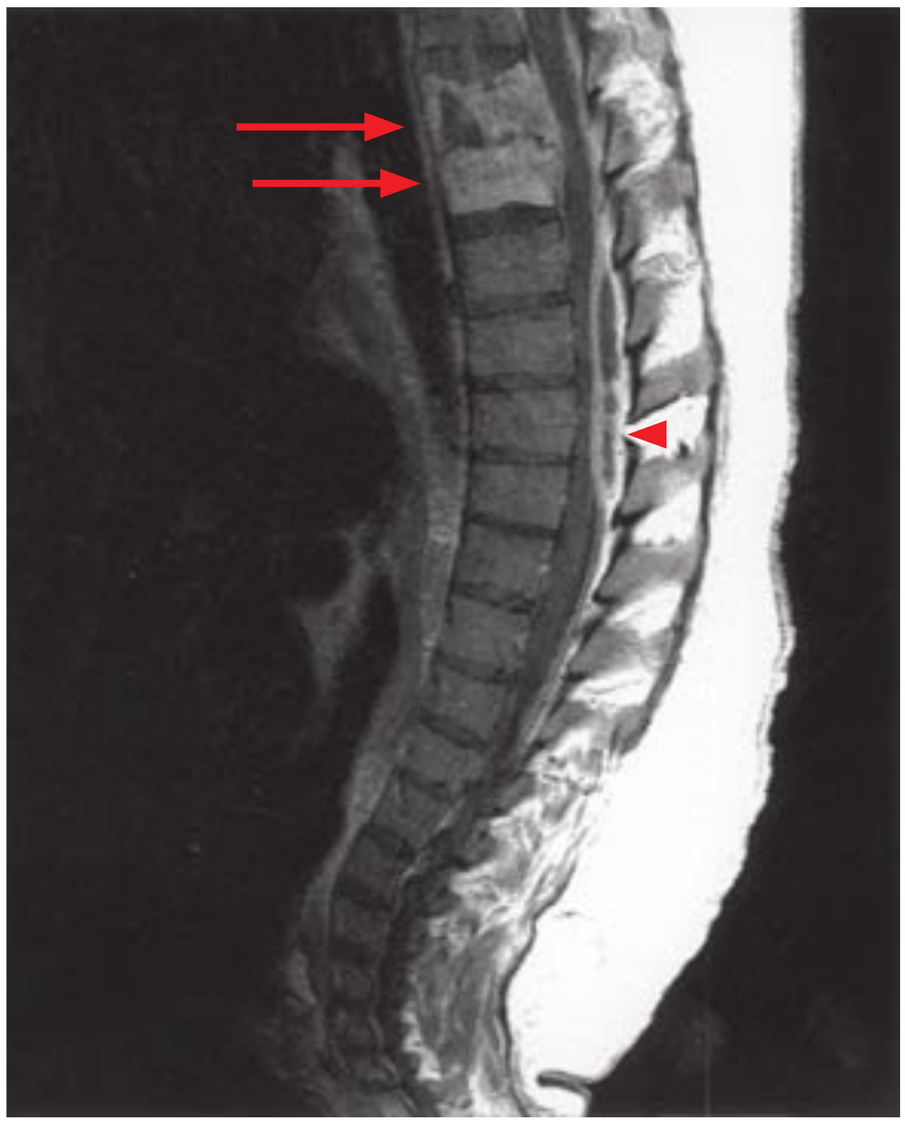


FIGURE 2.8-38. Diskitis/osteomyelitis. Sagittal contrast-enhanced MRI shows destruction of a lower thoracic intervertebral disk with abnormal enhancement throughout the adjacent vertebral bodies (arrows) and a posterior rim-enhancing epidural abscess (arrowhead) in the spinal canal. (Reproduced with permission from Tintinalli JE et al. Tintinalli's Emergency Medicine: A Comprehensive Study Guide, 6th ed. New York, NY: McGraw-Hill; 2004.)

Complications

Chronic osteomyelitis, sepsis, septic arthritis. Long-standing chronic osteomyelitis with a draining sinus tract may eventually lead to **squamous cell carcinoma** (Marjolin ulcer).

A

Salmonella. S aureus is the most common cause in patients without sickle cell disease and is the second most common organism that causes osteomyelitis in patients with sickle cell disease.

HIGH-YIELD FACTS IN

MUSCULOSKELETAL

Common Adult Orthopedic Injuries 236

Common Peripheral Nerve Injuries 238

Compartment Syndrome 238

Carpal Tunnel Syndrome 239

Bursitis 240

Tendinitis 241

Low Back Pain 241

- Herniated disk 241
- Spinal Stenosis 242

Osteosarcoma 243

Septic Arthritis 244

Osteoarthritis 244

Gout 246

Rheumatoid Arthritis 247

Seronegative Spondyloarthropathy 249

- Ankylosing Spondylitis 249

Polymyositis and Dermatomyositis 249

Systemic Sclerosis 250

Systemic Lupus Erythematosus 252

Giant Cell Arteritis 253

Complex Regional Pain Syndrome 253

Fibromyalgia 254

Polymyalgia Rheumatica 254

Common Adult Orthopedic Injuries

Table 2.9-1 outlines the presentation and treatment of orthopedic injuries that commonly affect adults (see Figures 2.9-1 through 2.9-4).

TABLE 2.9-1. Common Adult Orthopedic Injuries

Upper Extremity		
Injury	**Presentation**	**Treatment**
Shoulder dislocation	**Anterior dislocation:** Most common; risk of **axillary nerve injury.** Patients hold arm in slight **abduction and external rotation** (see Figure 2.9-1). **Posterior dislocation:** Rare; associated with **seizure and electrocution.** Patients hold arm in **adduction and internal rotation.**	Reduction followed by a sling and swath. Recurrent dislocations may need surgical treatment.
Humerus fracture	Direct trauma. **Radial nerve palsy** may lead to wrist drop and loss of thumb extension.	Hanging-arm cast vs coaptation splint and sling. Functional bracing.
"Nightstick fracture"	**Ulnar shaft** fracture from direct trauma often in self-defense against a blunt object.	ORIF if significa tly displaced.
Monteggia fracture	Diaphyseal fracture of the **proximal ulna** with **subluxation of the radial head.** Results from fall on pronated and outstretched arm.	ORIF of the shaft fracture and closed reduction of the radial head.
Galeazzi fracture	Diaphyseal fracture of the **radius** with **dislocation of the distal radioulnar joint.** Results from a direct blow to the radius.	ORIF of the radius and casting of the fractured forearm in supination to reduce the distal radioulnar joint.
Colles fracture	Involves the **distal radius.** Often results from a **fall onto an outstretched hand,** leading to a **dorsally displaced, dorsally angulated fracture.** Commonly seen in the elderly (osteoporosis) and children.	Closed reduction followed by application of a long-arm cast; open reduction if the fracture is intra-articular.
Scaphoid fracture	**Most commonly fractured carpal bone. Results from a fall onto an outstretched hand.** May take 2 weeks for radiographs to show fracture (see Figure 2.9-2). Assume a fracture if there is **tenderness in anatomic snuff ox with axial loading.**	Thumb spica cast. If displacement or scaphoid nonunion is present, treat with open reduction. With proximal-third fractures, **AVN may result** from disruption of blood fl w.
Boxer's fracture	Fracture of the **fi th metacarpal neck.** Due to forward trauma of a closed fist (e , punching a wall).	Closed reduction and ulnar gutter splint; percutaneous pinning if the fracture is excessively angulated.

(continues)

TABLE 2.9-1. Common Adult Orthopedic Injuries (continued)

Lower Extremity		
Injury	**Presentation**	**Treatment**
Hip dislocation	**Posterior dislocation:** Most common (> 90%); occurs via a posteriorly directed force on an internally rotated, flexed, adducted hip **("dashboard injury").** Associated with a risk of **sciatic nerve injury** and **AVN** (see Figure 2.9-3). **Anterior dislocation:** Can injure the **obturator nerve.**	Closed reduction followed by abduction pillow/bracing. Evaluate with CT scan after reduction.
Hip fracture	↑ risk with osteoporosis. Presents with a **shortened and externally rotated** leg. Can be radiographically occult, so a good clinical history with ⊖ radiographs warrants further evaluation with CT or MRI. **Displaced femoral neck fractures** associated with an ↑ **risk of AVN** and nonunion. Associated with **DVTs.**	ORIF. Displaced femoral neck fractures in elderly patients may require a hip hemiarthroplasty or total arthroplasty. **Anticoagulate to ↓ the likelihood of DVTs.** Hip fracture involves the acetabulum and/or the proximal intracapsular femur.
Femoral fracture	Direct trauma. Beware of **fat emboli,** which present with fever, changes in mental status, dyspnea, hypoxia, petechiae, and ↓ platelets.	Intramedullary nailing of the femur. Irrigate and debride open fractures.
Knee injuries	Present with knee instability and hematoma. **ACL:** ▪ Result from a noncontact **twisting mechanism, forced hyperextension, or impact to an extended knee.** ▪ ⊕ anterior drawer and Lachman tests. ▪ Rule out a meniscal or MCL injury (MCL injury = ⊕ valgus stress test; LCL injury = ⊕ varus stress test). **PCL:** ▪ Result from a **posteriorly directed force on a flexed knee** (eg, dashboard injury). ▪ ⊕ posterior drawer test. **Meniscal tears:** ▪ Result from an **acute twisting injury or a degenerative tear** in elderly patients. ▪ Clicking or locking may be present. ▪ Examination shows joint line tenderness and a ⊕ McMurray test.	MRI is the diagnostic test of choice. Treatment of MCL/LCL and meniscal tears can be **conservative.** Treatment of ACL injuries in active patients is generally **surgical** with graft from the patellar or hamstring tendons. Operative PCL reconstruction is reserved for highly competitive athletes with high-grade injuries. Operative meniscal repair is for younger patients with reparable tears or older patients with mechanical symptoms who do not respond to conservative treatment.
Tibial fracture	Direct trauma. Watch for compartment syndrome.	Casting vs intramedullary nailing vs ORIF.
Achilles tendon rupture	Presents with a **sudden "pop"** like a rifle shot. More likely with ↓ physical conditioning. Limited plantar flexion and a ⊕ Thompson test (pressure on the gastrocnemius leading to absent foot plantar flexion).	Surgery followed by a long-leg cast for 6 weeks.



A B

FIGURE 2.9-1. Anterior shoulder dislocation. AP **(A)** and scapular Y **(B)** radiographs of the right shoulder demonstrate anterior and inferior dislocation of the humeral head relative to the glenoid. (Reproduced with permission from USMLE-Rx.com.)



FIGURE 2.9-2. Scaphoid fracture. PA radiograph of the right wrist shows a fracture (arrow) through the waist of the scaphoid. (Reproduced with permission from USMLE-Rx.com.)



FIGURE 2.9-3. Posterior hip dislocation. Posterior hip dislocation with concomitant fracture of the posterior wall and dome of the acetabulum. (Reproduced with permission from Doherty GM. Current Diagnosis &Treatment: Surgery, 13th ed. New York, NY: McGraw-Hill; 2010.)

Common Peripheral Nerve Injuries

Table 2.9-2 outlines the clinical findings of the most common peripheral nerve injuries.

Compartment Syndrome

↑ **pressure** within a confined space that compromises nerve, muscle, and soft tissue perfusion. Occurs primarily in the anterior compartment of the lower leg and in forearm 2° to trauma to the affected limb (fracture or muscle injury). Also a concern with circumferential thermal injury and after surgical procedures.

History/Pe

- Presents with pain out of proportion to physical findings; **pain with passive motion** of the fingers and toes; and **p**aresthesias, **p**allor, **p**oikilothermia, **p**ulselessness, and **p**aralysis (the **6 P's**).
- Paralysis and pulselessness occur as **late** signs of compartment syndrome!

Diagnosis

Based on history, exam, and elevated compartment pressures (although not necessary). Calculate delta pressures (diastolic pressure – compartment pressure); ⊕ if delta pressure ≤ 30 mm Hg).

Treatment

Immediate fasciotomy to ↓ pressures and ↑ tissue perfusion.



A B C

FIGURE 2.9-4. Forearm fractures. (A) Monteggia; **(B)** Galeazzi; **(C)** Colles. (Parts A, B reproduced with permission from Knoop K et al., eds. The Atlas of Emergency Medicine, 3rd ed. New York, NY: McGraw-Hill; 2009. Part C reproduced with permission from Usatine RP et al., eds. The Color Atlas of Family Medicine, 2nd ed. New York, NY: McGraw-Hill; 2013.)

Carpal Tunnel Syndrome

Entrapment of the median nerve at the wrist caused by ↓ size or space of the carpal tunnel, leading to paresthesias, pain, and occasionally paralysis. Can be precipitated by overuse of wrist flexors; associated with diabetes mellitus or thyroid dysfunction. Commonly occurs in pregnant and middle-aged women.

History/PE

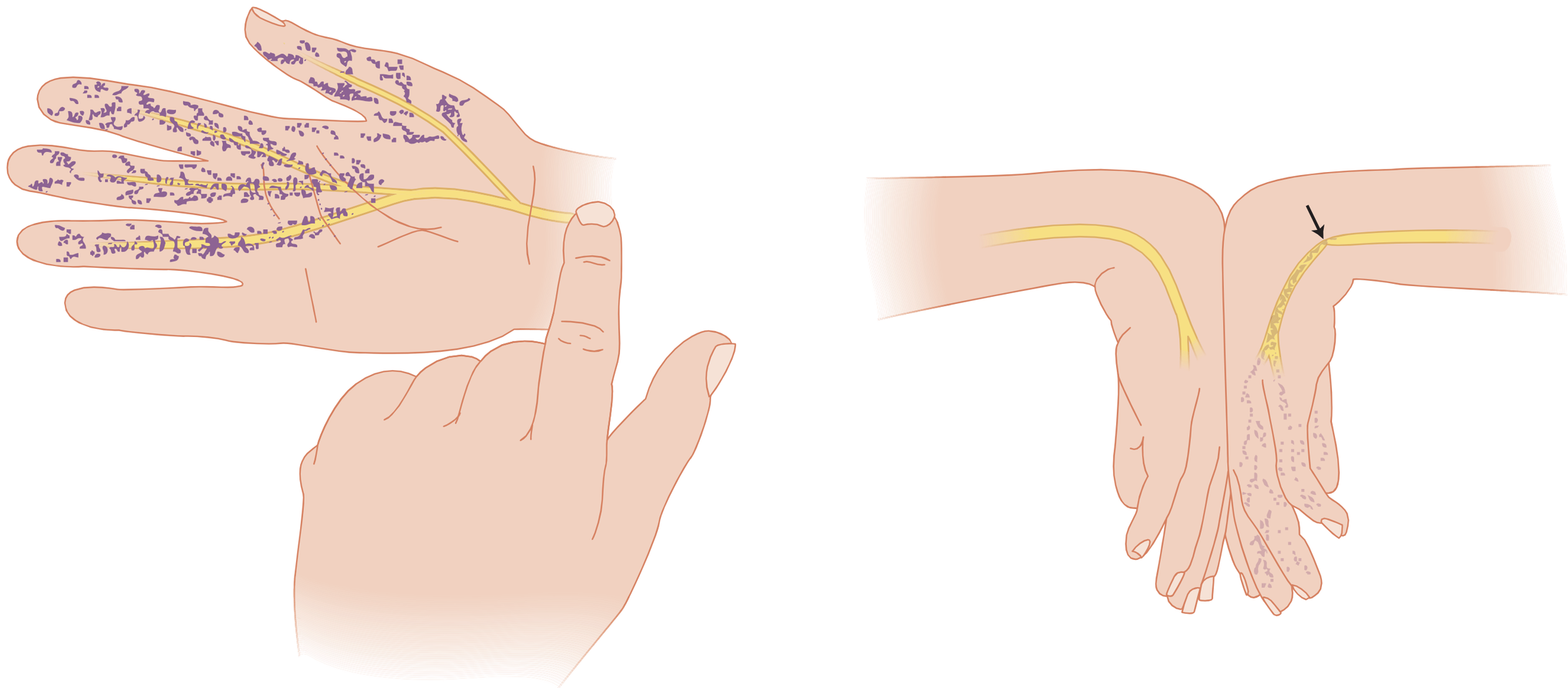
- Presents with aching over the **thenar area of the hand** and proximal forearm.
- Paresthesias or numbness is seen in a median nerve distribution.
- Symptoms **worsen at night,** when the wrists are held in flexion, or with repetitive hand use.
- Examination shows thenar atrophy (if CTS is long-standing).
- **Phalen maneuver** and **Tinel sign** are ⊕ (see Figure 2.9-5).

KEY FACT

Open fractures are an orthopedic emergency. Patients should be taken to the OR within 8–24 hours for irrigation and debridement followed by fracture repair. Reduce infection risk with antibiotics and tetanus prophylaxis.

TABLE 2.9-2. Common Peripheral Nerve Injuries

Nerve	Motor deficit	Sensory deficit	Common causes	Clinical findings
Radial	Wrist extension.	Dorsal forearm and hand (the first 3 fingers	Humeral fracture. Prolonged compression at level of humerus **("Saturday night palsy").**	**Wrist drop.**
Median	Forearm pronation, thumb opposition.	Palmar surface (the first 3 fingers)	Carpal tunnel.	**Weak wrist flexion** and **flat thenar eminence.**
Ulnar	Finger abduction.	Palmar and dorsal surface (the last 2 fingers)	Elbow dislocation.	**Claw hand.**
Axillary	Arm abduction.	**↓ sensation over the deltoid.**	**Anterior** shoulder dislocation.	
Peroneal	Dorsiflexion, eversion.	Dorsal foot and lateral leg.	Knee dislocation. Trauma to the fibula	**Foot drop.**



A B

FIGURE 2.9-5. Carpal tunnel syndrome. (A) Tinel sign. The Tinel test is performed by tapping the volar surface of the wrist over the median nerve. **(B)** Phalen maneuver. The Phalen maneuver is performed by compressing the opposing dorsal surfaces of the hand with the wrists flexed together as shown. This causes tingling over the median nerve distribution. (Reproduced with permission from Simon RR, Sherman SC, Koenigsknecht SJ. Wrist. Emergency Orthopedics: The Extremities, 5th ed. New York, NY: McGraw-Hill; 2007; as published in Tintinalli JE et al. Tintinalli's Emergency Medicine: A Comprehensive Study Guide, 7th ed. New York, NY: McGraw-Hill; 2010.)

KEY FACT

Posterior hip dislocation:
Shortened, internally rotated leg.
Anterior hip dislocation:
Lengthened, externally rotated leg.
Hip fracture: Shortened, externally rotated leg.

KEY FACT

The "classic" **unhappy triad** of knee injury involves the ACL, the MCL, and the medial meniscus. However, **lateral** meniscal tears are more commonly seen in **acute** ACL injuries.

KEY FACT

Median nerve injury leads to the "Benediction sign" due to an inability to **close** the first through third digits. Ulnar nerve injury leads to the "claw hand" due to an inability to **open** the fourth to fifth digits.

Diagnosis

A clinical diagnosis, although nerve conduction studies and EMG testing can be used to confirm.

Treatment

- Splint the wrist in a neutral position at night and during the day if possible.
- Conservative treatment can include corticosteroid injection of the carpal canal.
- Surgical release of the carpal tunnel is a widely accepted treatment, particularly for fixed sensory loss, thenar weakness, or intolerable symptoms with no improvement after splinting and/or glucocorticoids.

Complications

Permanent loss of sensation, hand strength, and fine motor skills.

Bursitis

Inflammation of the bursae by **repetitive use, trauma, infection, systemic inflammatory disease (eg, autoimmune disease), or microcrystalline disorders (eg, gout).** A bursa is a flattened sac filled with a small amount of synovial fluid that serves as a protective buffer between bones and overlapping muscles. Common sites of bursitis include subacromial, olecranon, trochanteric, prepatellar, and infrapatellar bursae.

History/Pe

Presents with localized tenderness, ↓ range of motion (ROM), edema, and erythema; patients may have a history of trauma or inflammatory disease.

Diagnosis

Needle aspiration is indicated if septic bursitis is suspected; may also help with diagnosis of crystal deposition disorder. No labs or imaging is needed.

Treatment

- Conservative treatment includes rest, heat and ice, elevation, and NSAIDs.
- Intrabursal corticosteroid injection can be considered but is **contraindicated if septic bursitis** is suspected.
- Septic bursitis should be treated with 7–10 days of antibiotics.

Tendinitis

An **inflammatory condition** characterized by pain at tendinous insertions into bone associated with swelling or impaired function. It commonly occurs in the supraspinatus, **biceps,** wrist extensor, **patellar,** iliotibial band, posterior tibial, and **Achilles tendons.** Overuse is the most common cause.

History/Pe

- Presents with pain at a tendinous insertion that worsens with **repetitive stress** and **resisted strength testing** of the affected muscle group.
- Lateral epicondylitis (or tennis elbow) worsens with resisted extension of the wrist, and medial epicondylitis with resisted flexion of the wrist.

Diagnosis

A clinical diagnosis. Consider a radiograph if there is a history of trauma. MRI and ultrasonography may be useful in detecting tendon tears.

Treatment

- Treat with rest and NSAIDs; apply ice for the first 24–48 hours.
- Consider splinting, bracing, or immobilization.
- Begin strengthening exercises once pain has subsided.
- If conservative treatment fails, consider corticosteroid injection. **Never inject the Achilles tendon** in view of the ↑ risk of rupture. Avoid repetitive injection.

Low Back Pain

Low back pain is the second-leading symptom-related cause for office visits in the United States. Though often self-limited, it can be also be a sign of more severe disease, including infection, malignancy, or AAA.

HERNIATED DISK

Causes include degenerative changes, trauma, or neck/back strain or sprain. Most common (95%) in the lumbar region, especially at **L5–S1** (most common site) and L4–L5 (second most common site).

History/Pe

- Presents with sudden onset of severe, electricity-like LBP, usually preceded by several months of aching, "discogenic" pain.

KEY FACT

Volkmann contracture of the wrist and fingers is caused by compartment syndrome, which is associated with supracondylar humerus fractures. Ischemia results in fibrosis of dead muscle.

KEY FACT

Infection of the superficial bursae occurs after trauma to the skin. Infection of deep bursae is often iatrogenic following injections or aspirations.

KEY FACT

Oral fluoroquinolones are associated with an ↑ risk of tendon rupture and tendinitis.

Q 1

A 23-year-old man presents to the ED with a swollen and erythematous right hand following an altercation at a bar a few days ago. The dorsum of the hand shows abrasions, and x-ray films reveal a fracture of the fifth metacarpal. What is the next step in management?

Q 2

A 37-year-old man is seen after a motorcycle accident. He complains of intense leg pain, tingling in his foot, and inability to move his toes. Examination reveals pain with passive motion of his toes and palpable dorsalis pedis pulses. An x-ray film confirms a tibial fracture. What is the best treatment?

KEY FACT

Tendinitis is a slight misnomer, as a classic cellular inflammatory response is absent or minimal in cases of overuse tendinopathy. Tendinosis is a more appropriate term referring to chronic tendinopathy without cellular inflammation.

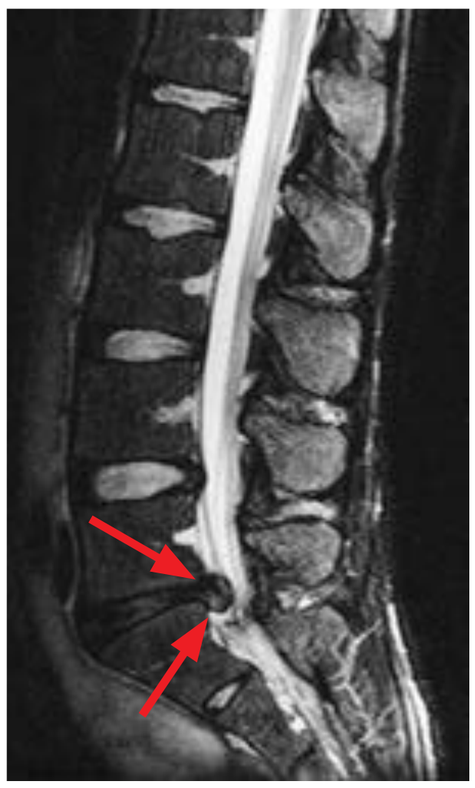


FIGURE 2.9-6. Disk herniation. Sagittal T2-weighted MRI of the lumbar spine shows posterior herniation of the L5–S1 disk. (Reproduced with permission from Fauci AS et al. Harrison's Principles of Internal Medicine, 17th ed. New York, NY: McGraw-Hill; 2008.)

1 A

If skin is broken in a boxer's fracture, assume infection by human oral pathogens and treat with surgical irrigation, debridement, and IV antibiotics to cover for Eikenella.

2 A

Immediate fasciotomy for compartment syndrome (within 6 hours to prevent muscle necrosis) followed by fracture stabilization. Remember that nonpalpable pulses are a late finding.

- Common among middle-aged and older men.
- Exacerbated by ↑ intra-abdominal pressure or Valsalva (eg, coughing).
- Associated with **sciatica,** paresthesias, muscle weakness, atrophy, contractions, or spasms.
- A **passive straight-leg raise ↑ pain** (highly sensitive but not specific).
- A crossed straight-leg raise ↑ pain (highly specific but not sensitive). Large midline herniations can cause **cauda equina syndrome.**

Diagnosis

- Obtain an ESR and a plain radiograph if other causes of back pain are suspected (eg, infection, trauma, compression fracture). X-ray film may show disk herniation (see Figure 2.9-6).
- Order a stat MRI for cauda equina syndrome or for a severe or rapidly progressing neurologic deficit.
- Order an MRI if symptoms are refractory to conservative management.

Treatment

- **NSAIDs** in scheduled doses, physical therapy, and local heat lead to resolution within 4 weeks in 80% of cases. Do not prescribe bed rest; **continuation of regular activities** is preferred.
- Epidural injection or nerve block may be of benefit.
- Severe or rapidly evolving neurologic deficits and cauda equina syndrome are indications for surgical intervention.

SPINAL STENOSIS

Narrowing of the lumbar or cervical spinal canal, leading to compression of the nerve roots and spinal cord. Most commonly due to degenerative joint disease; typically occurs in middle-aged or elderly patients.

History/Pe

- Presents with neck pain, back pain that **radiates to the arms or the buttocks and legs,** and leg numbness/weakness.
- In lumbar stenosis, leg cramping is worse with standing and with walking.
- In lumbar stenosis, symptoms **improve** with **flexion at the hips** and bending forward, which relieves pressure on the nerves.

Diagnosis

- Radiographs show degenerative changes that include disk space narrowing, facet hypertrophy, and sometimes spondylolisthesis, leading to a narrowed spinal canal.
- MRI or CT shows spinal stenosis.

Treatment

- **Mild to moderate:** NSAIDs and abdominal muscle strengthening.
- **Advanced:** Epidural corticosteroid injections can provide relief.
- **Refractory:** Surgical laminectomy may achieve significant short-term success, but many patients will have a recurrence of symptoms.

Table 2.9-3 outlines the motor, reflex, and sensory deficits with which LBP is associated.

TABLE 2.9-3. Motor and Sensory Deficits in Back Pain

	Associated Deficit		
Nerve Root	Motor	Reflex	Sensory
L4	Foot dorsiflexion (tibialis anterior).	Patellar	Medial aspect of the lower leg.
L5	Big toe dorsiflexion (extensor hallucis longus), foot eversion (peroneus muscles).	None	Dorsum of the foot and lateral aspect of the lower leg.
S1	Plantar flexion (gastrocnemius/soleus), hip extension (gluteus maximus).	Achilles	Plantar and lateral aspects of the foot.

Osteosarcoma

Although a rare tumor, it is the most common primary malignancy of bone for children and adolescents. Tends to occur in the **metaphyseal** regions of the **distal femur, proximal tibia,** and proximal humerus; often metastasizes to the lungs. In adults, osteosarcoma is often a result of sarcomatous transformation of other benign tumors, including Paget disease.

History/Pe

- Presents as progressive and eventually intractable **pain that worsens at night.**
- Constitutional symptoms such as fever, weight loss, and night sweats may be present.
- Erythema and enlargement over the site of the tumor may be seen.

See the Endocrinology chapter for a discussion of osteosarcoma vs Paget disease.

Diagnosis

- Radiographs can show **Codman triangle** (periosteal new-bone formation at the diaphyseal end of the lesion) or a **"sunburst pattern"** of the osteosarcoma (see Figure 2.9-7)—in contrast to the multilayered **"onion skinning"** that is classic for Ewing sarcoma and the **"soap bubble"** appearance of giant cell tumor of bone (see Figure 2.9-8).
- Once suspicion for bone malignancy is high, a biopsy is useful for confirming diagnosis.
- MRI and CT of the chest facilitate staging (soft tissue and bony invasion) and planning for surgery.

Treatment

- Limb-sparing surgical procedures and pre- and postoperative chemotherapy (eg, methotrexate, doxorubicin, cisplatin, ifosfamide).
- Amputation may be necessary.

KEY FACT

Most LBP is mechanical, **so bed rest is contraindicated.**

KEY FACT

Red flags for LBP include age > 50, > 6 weeks of pain, a previous cancer history, severe pain, constitutional symptoms, neurologic deficits, and loss of anal sphincter tone.

KEY FACT

Bowel or bladder dysfunction (urinary overflow incontinence), impotence, and saddle-area anesthesia are consistent with cauda equina syndrome, which is a surgical emergency.

KEY FACT

The most common benign bone tumor is osteochondroma.

Q 1

A 55-year-old man with a history of prostate cancer presents with LBP and bilateral leg weakness. On examination, he is found to have point tenderness on the lumbar spine and ↓ sensation in his legs. What is the best next step?

Q 2

A 15-year-old youth presents with several month history of pain in the upper part of his thigh. The pain is worse at night. A plain film shows a small nidus of lucency. What OTC remedy is indicated?



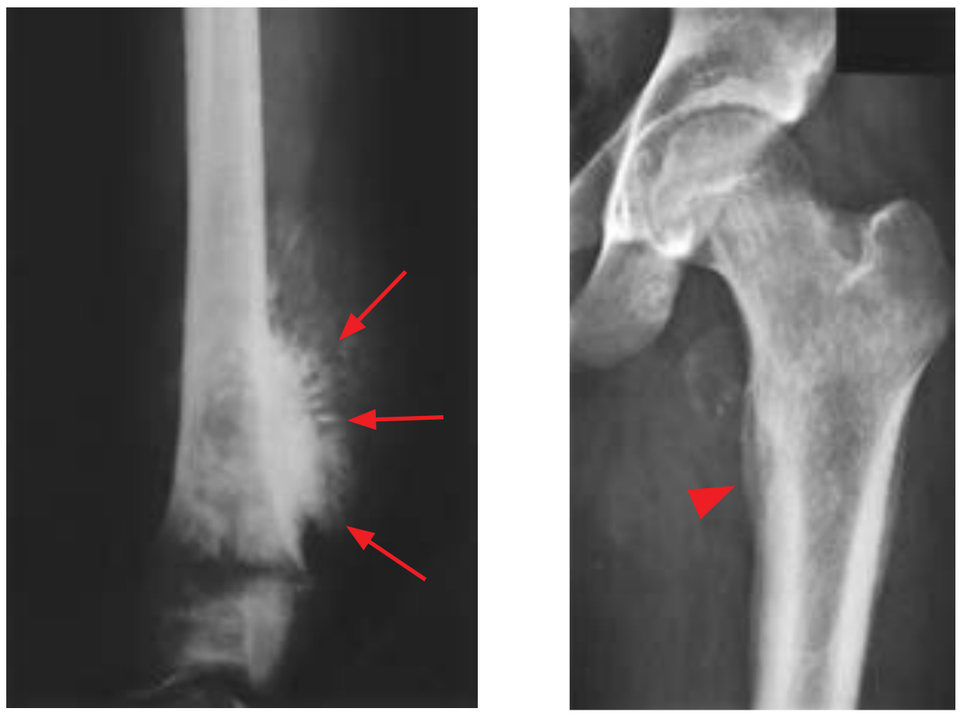
FIGURE 2.9-8. Giant cell tumor of the bone. Note the "soap bubble" appearance at the proximal end of the tibia. The distal end of the femur (not shown) is another common location. (Reproduced with permission from Skinner HB. Current Diagnosis & Treatment in Orthopedics, 4th ed. New York, NY: McGraw-Hill; 2006.)

1 A

Give steroids to relieve spinal cord compression resulting from likely bone metastasis. MRI is the best study, but preventing permanent neurologic disability is more important at this time. Remember to consider multiple myeloma, which can present almost identically.

2 A

This adolescent patient is likely presenting with osteoid osteoma, a benign bone-forming tumor characterized by prostaglandin formation. Relief of pain is thus often achieved with NSAIDs. Tumors may self-resolve, but surgical removal of the nidus may be necessary for symptom relief.



A B

FIGURE 2.9-7. Malignant bone tumors. (A) Osteosarcoma. Femoral radiograph shows the typical "sunburst" appearance of osteosarcoma (arrows). **(B) Ewing sarcoma.** The characteristic "onion skinning" of Ewing sarcoma (arrowhead) is evident in the proximal femur in this radiograph of the left hip. (Reproduced with permission from Kantarjian HM et al. MD Anderson Manual of Medical Oncology, 1st ed. New York, NY: McGraw-Hill; 2006.)

Septic Arthritis

An infection of the joint space that can occur after open injury or bacteremia. Prosthetic joints greatly ↑ the risk. Rheumatoid arthritis (RA), osteoarthritis (OA), and bacteremia from endocarditis and IV drug use are also risk factors (see below).

History/Pe

Presents as a warm, red, immobile joint. Palpable effusions may also be present. Fevers and chills can be seen if the patient is bacteremic.

Diagnosis

- The best test is **joint aspiration.** See Table 2.9-4.
- A **WBC count > 80,000 mm³,** ⊕ Gram stain, or ⊕ fluid culture.
- The most common organisms are Staphylococcus, Streptococcus, and gram-⊖ rods.

Treatment

Empirically treat with **ceftriaxone and vancomycin** until cultures come back; then modify therapy for specific organisms. Septic joints are treated with **surgical debridement** or serial aspirations.

Osteoarthritis

A common, chronic, noninflammatory arthritis of the synovial joints. Characterized by deterioration of the articular cartilage and osteophyte bone formation at the joint surfaces. Risk factors include a ⊕ family history, **obesity,** and a **history of joint trauma.** Table 2.9-5 contrasts OA with RA.

TABLE 2.9-4 Synovial Fluid Analysis

	Normal	Noninflammatory	Inflammatory[a]	Septic
Color	Clear	Yellow	Yellow	Yellow-green
Viscosity	High	High	Low	Variable
WBC, per mm^3	< 200	0–1000	1000–10,000 (up to 100,000)	10,000–100,000
PMN (%)	< 25	< 25	≥ 50	≥ 75
Glucose, mg/dL	= serum	= serum	> 25	< 25
			(Crystal analysis for gout/ pseudogout)	

[a]A joint affected by inflammatory arthritis can become secondarily infected.

History/PE

Presents with **crepitus,** ↓ ROM, and initially **pain that worsens with activity and weight bearing but improves with rest.** Morning stiffness generally lasts for < 30 minutes. Stiffness is also experienced after periods of rest ("gelling").

Diagnosis

- Radiographs show **joint space narrowing,** osteophytes, subchondral sclerosis, and subchondral bone cysts (see Figure 2.9-9). Radiograph severity does not correlate with symptomatology.
- Synovial fluid shows straw-colored fluid, normal viscosity, and a WBC count < 2000 cells/μL.
- Laboratory tests, including inflammatory markers, are typically **normal.**

Treatment

- Physical therapy, **weight reduction,** and **NSAIDs.** Intra-articular corticosteroid injections may provide temporary relief.

TABLE 2.9-5. Osteoarthritis vs Rheumatoid Arthritis

Variable	Osteoarthritis	Rheumatoid arthritis
History	Affects the elderly; has slow onset. Pain **worsens with use.**	Affects the young; presents with morning stiffness that **improves with use.**
Joint involvement	Affects the **DIP, PIP,** hips, and knees.	Affects the **wrists, MCP,** ankles, knees, shoulders, hips, and elbows. Has a **symmetric** distribution.
Synovial fluid analysis and imaging	WBC count < 2000 cells/mm^3; osteophytes. Joint space narrowing is seen on x-ray.	Anti-CCP antibodies.

KEY FACT

Classic findings of **Ewing sarcoma:** 10–20 years of age with a multilayered "onion-skinning" finding on x-ray in the diaphyseal regions of the femur. "Eat **wings** and **onion** rings."

KEY FACT

Classic findings of a **giant cell tumor of bone:** a woman 20–40 years of age presenting with knee pain and a mass, along with a "soap bubble" appearance on x-ray in the epiphyseal/metaphyseal region of long bones.

KEY FACT

In sexually active individuals with joint pain, consider gonococcal septic arthritis. Neisseria gonorrhoeae septic arthritis can present with asymmetric oligoarthritis, tenosynovitis, and skin rash.

KEY FACT

An elevated white count in synovial fluid can be either inflammatory or infectious in etiology.

KEY FACT

Rheumatoid arthritis = MCP joints; **O**steoarthritis = PIP joints (**B**ouchard nodes) and DIP joints (**H**eberden nodes).
"**O**uch, my **B**ad **H**ands."

KEY FACT

In a child with gout and inexplicable injuries, consider Lesch-Nyhan syndrome.

KEY FACT

Gout crystals appear ye**LL**ow when para**LL**el to the condenser.

KEY FACT

Causes of hyperuricemia:

- ↑ cell turnover (hemolysis, blast crisis, tumor lysis, myelodysplasia, psoriasis)
- Cyclosporine
- Dehydration
- Diabetes insipidus
- Diet (eg, ↑ red meat, alcohol)
- Diuretics
- Lead poisoning
- Lesch-Nyhan syndrome
- Salicylates (low dose)
- Starvation



FIGURE 2.9-9. Osteoarthritis. Plain radiographs show joint space narrowing, osteophytes, and subchondral degenerative cysts involving the DIP and PIP joints, with sparing of the MCP. (Reproduced with permission from USMLE-Rx.com.)

- Consider **joint replacement** (eg, total hip/knee arthroplasty) in advanced cases.

Gout

Recurrent attacks of **acute monoarticular arthritis** resulting from intra-articular deposition of **monosodium urate crystals** due to disorders of urate metabolism. Risk factors include male gender, obesity, postmenopausal status in women, and **binge drinking.**

History/Pe

- Presents with excruciating joint pain of sudden onset.
- Most commonly affects the **first MTP joint** (podagra) and the midfoot, knees, ankles, and wrists; the hips and shoulders are generally spared.
- Joints are erythematous, swollen, and exquisitely tender.
- **Tophi** (urate crystal deposits in soft tissue) can be seen with chronic disease (see Figure 2.9-10). Tophi can ulcerate and drain a chalky white.
- Uric acid kidney stones are seen with chronic disease.

Diagnosis

- Joint fluid aspirate shows **needle-shaped, negatively birefringent crystals** (vs pseudogout; see Table 2.9-6).
- Serum uric acid is usually ↑ (≥ 7.5 mg/dL), but patients may have normal levels.
- Punched-out erosions with overhanging cortical bone **("rat-bite" erosions)** are seen in advanced gout.



FIGURE 2.9-10. Tophaceous gout. Note the slowly enlarging nodule of the right second toe in a 55-year-old alcoholic, hypertensive man on hydrochlorothiazide. (Reproduced with permission from USMLE-Rx.com.)

Treatment

- **Acute attacks:**
  - High-dose **NSAIDs** (eg, indomethacin) are first line. Colchicine may also be used but is inferior to NSAIDs.
  - **Steroids** are used when NSAIDs are ineffective or contraindicated, as in renal disease.
- **Maintenance therapy:**
  - **Allopurinol** for overproducers, those with contraindications to probenecid treatment (tophi, renal stones, chronic kidney disease), and refractory cases; **probenecid** for under-secreters.
  - Allopurinol can ↓ the incidence of **acute urate nephropathy.**
- Weight loss and avoidance of triggers of hyperuricemia will prevent recurrent attacks in many patients. **Avoid alcohol consumption.**

KEY FACT

Colchicine inhibits neutrophil chemotaxis and is most effective when used early during a gout flare. However, it can cause diarrhea and bone marrow suppression (neutropenia).

Rheumatoid Arthritis

A systemic autoimmune disorder characterized by chronic, destructive, inflammatory arthritis with **symmetric** joint involvement that results in synovial hypertrophy and pannus formation, ultimately leading to erosion of adjacent cartilage, bone, and tendons. Risk factors include female gender, age 35–50, and **HLA-DR4.**

TABLE 2.9-6. Gout vs Pseudogout

Disorder	History	Physical Findings	Crystal Shape	Crystal Birefringence
Gout (uric acid)	Male, binge drinking, acute onset afterward.	The first big toe is affected.	Needle shaped.	⊖
Pseudogout: CPPD	Hemochromatosis or hyperparathyroidism.	The wrists and knees are affected.	Rhomboid.	⊕

History/Pe

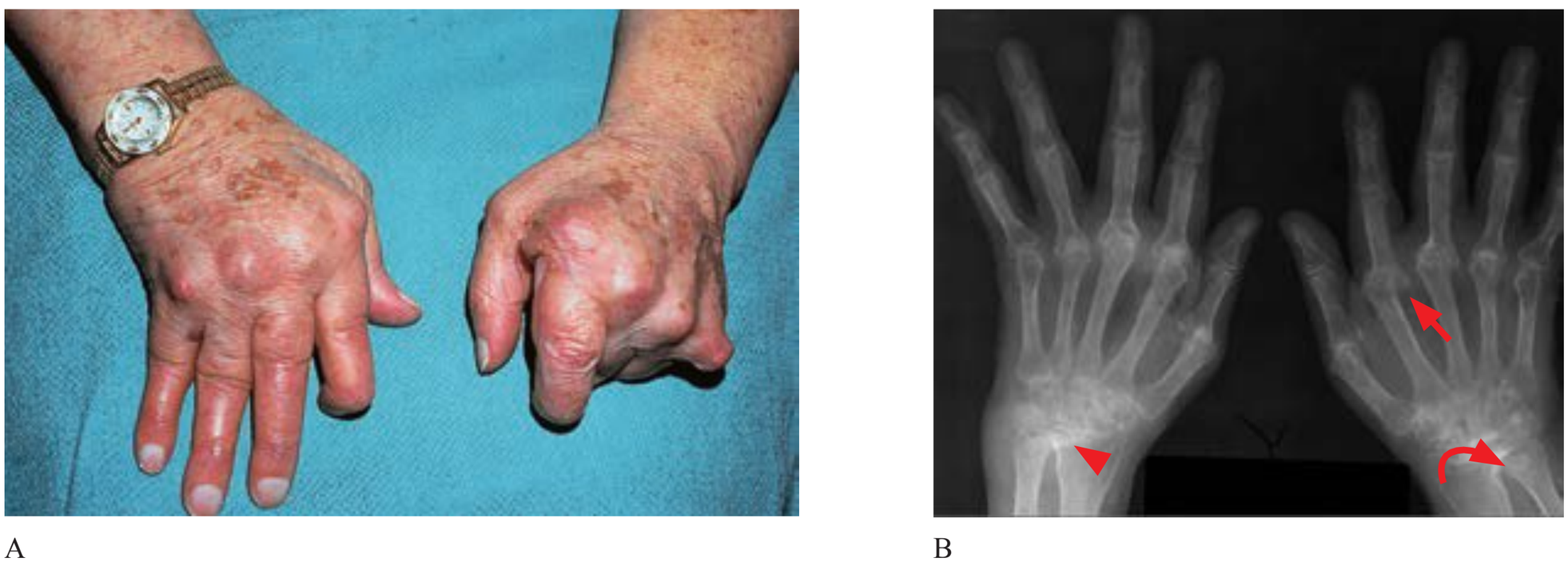
- Insidious onset of **morning stiffness** for > 1 hour along with painful, warm swelling of multiple symmetric joints (**wrists, MCP joints,** ankles, knees, shoulders, hips, and elbows) for > 6 weeks.
- In late cases, ulnar deviation of the fingers is seen with MCP joint hypertrophy (see Figure 2.9-11A).
- Also presents with ligament and tendon **deformations** (eg, swan-neck and boutonnière deformities), vasculitis, atlantoaxial subluxation (intubation risk), and keratoconjunctivitis sicca.

Diagnosis

- **Diagnostic criteria:**
  - ↑ **rheumatoid factor (RF)** (IgM antibodies against Fc IgG) or the presence of **anti-CCP** antibodies.
  - ↑ ESR or CRP may also be seen.
  - Exclusion of acute, autoimmune, or crystalline causes.
  - Inflammatory arthritis of three or more joints for > 6 weeks.
- **Labs:**
  - Anemia of chronic disease is common.
  - Synovial fluid aspirate shows turbid fluid, ↓ viscosity, and an ↑ WBC count (3000–50,000 cells/μL).
- **Radiographs:**
  - **Early:** Soft tissue swelling and juxta-articular demineralization.
  - **Late:** Symmetric joint space narrowing and erosions (see Figure 2.9-11B).

Treatment

- **NSAIDs:** Can be ↓ or discontinued following successful treatment with **disease-modifying antirheumatic drugs (DMARDs).**
- DMARDs should be started early and include **methotrexate** (the best initial DMARD to start with), hydroxychloroquine, and sulfasalazine. Second-line agents include TNF inhibitors, rituximab (anti-CD20), and leflunomide.



A B

FIGURE 2.9-11. Rheumatoid arthritis. (A) Note the typical ulnar deviation of the MCP joints and swelling of the MCP and PIP joints. Multiple subcutaneous rheumatoid nodules are also seen. **(B)** Hand radiograph shows symmetric erosions and joint space narrowing involving the MCP (arrow), carpal (arrowhead), and radioulnar (curved arrow) joints. Ulnar deviation at the MCP joint is also noted. (Part A reproduced with permission from Wolf K et al. Fitzpatrick's Dermatology in General Medicine, 7th ed. New York, NY: McGraw-Hill; 2008. Part B reproduced with permission from USMLE-Rx.com.)

Seronegative Spondyloarthropathy

ANKYLOSING SPONDYLITIS

A chronic inflammatory disease of the spine and pelvis that leads to fusion of the affected joints. Strongly associated with **HLA-B27.** Risk factors include male gender and a ⊕ family history.

History/Pe

- Typical onset is in the late teens and early 20s. Presents with fatigue, intermittent hip pain, and LBP that **worsens with inactivity and in the mornings.**
- ↓ spine flexion (⊕ Schober test), loss of lumbar lordosis, hip pain and stiffness, and ↓ chest expansion are seen as the disease progresses.
- Anterior **uveitis** and **heart block** can occur.
- Associated with enthesitis (pain at insertion of tendons/ligaments) at the heel.
- Other forms of seronegative spondyloarthropathy must be ruled out, including the following:
  - **Reactive arthritis** (formerly known as **Reiter syndrome**): A disease of young men. The characteristic arthritis, uveitis, conjunctivitis, and urethritis usually follow an infection with Campylobacter, Shigella, Salmonella, Chlamydia, or Ureaplasma.
  - **Psoriatic arthritis:** An oligoarthritis that can include the **DIP joints.** Associated with psoriatic skin changes and **sausage-shaped digits** (dactylitis). X-ray films show a classic "pencil in cup" deformity.
  - **Enteropathic spondylitis:** An ankylosing spondylitis–like disease characterized by sacroiliitis that is usually asymmetric and is associated with IBD.

KEY FACT

Reactive arthritis: "Can't see (uveitis), can't pee (urethritis), can't climb a tree (arthritis)."

Diagnosis

- ⊕ **HLA-B27** is found in 85–95% of cases.
- Radiographs may show **fused sacroiliac joints,** squaring of the lumbar vertebrae, development of vertical syndesmophytes, and **bamboo spine** (see Figure 2.9-12).
- ESR or CRP is ↑ in 75% of cases.
- ⊖ **RF;** ⊖ antinuclear antibody (ANA).

Treatment

- **NSAIDs** (eg, indomethacin) for pain; exercise to improve posture and breathing.
- **TNF inhibitors** or sulfasalazine can be used in refractory cases.



FIGURE 2.9-12. Ankylosing spondylitis. Frontal view of the thoracolumbar spine shows the classic "bamboo" appearance of the spine, which results from fusion of the vertebral bodies and posterior elements. (Reproduced with permission from Chen MY et al. Basic Radiology, 2nd ed. New York, NY: McGraw-Hill; 2011.)

Polymyositis and Dermatomyositis

Polymyositis is a progressive, systemic connective tissue disease characterized by immune-mediated striated muscle inflammation. **Dermatomyositis** presents with symptoms of polymyositis **plus** cutaneous involvement, although the pathogenesis is different. Most often affect patients 50–70 years of age; the male-to-female ratio is 1:2. Blacks are affected more often than whites. See also Table 2.9-7 and Figure 2.9-13.

TABLE 2.9-7. Polymyositis vs Dermatomyositis

polyMyoSitiS	dermatoMyoSitiS (Figure 2.9-13)
Symmetric. Progressive **proximal** muscle weakness and/or pain. Difficu y breathing or swallowing (advanced disease).	**+ rash.** **Heliotrope rash:** A violaceous periorbital rash. **"Shawl sign":** A rash involving the shoulders, upper chest, and back. **Gottron papules:** Papular rash with scales on the dorsa of the hands, over bony prominences.

KEY FACT

Keratoconjunctivitis sicca 2° to Sjögren syndrome is a common ocular manifestation of RA.

KEY FACT

Felty syndrome is characterized by RA, splenomegaly, and neutropenia.

KEY FACT

The DIP joint is spared in RA but is involved in OA.

KEY FACT

Hydroxychloroquine causes retinal toxicity.

History/Pe

- Patients may also develop myocarditis and cardiac conduction deficits.
- Can be associated with an underlying malignancy, especially lung and breast carcinoma.

Diagnosis

- ↑ **serum creatine kinase** and **anti-Jo-1 antibodies** can be seen (see Table 2.9-8).
- Diagnosis is generally made based on characteristic clinical and laboratory presentation without tissue biopsy; however, additional testing can be useful for atypical presentations.

Treatment

- High-dose corticosteroids with taper after 4–6 weeks to ↓ the maintenance dose.
- Azathioprine and/or methotrexate can be used as steroid-sparing agents.

Systemic Sclerosis

Also called scleroderma; characterized by inflammation that leads to progressive tissue fibrosis through excessive deposition of types I and III collagen. Commonly manifests as **CREST syndrome** (limited form) but can also occur



A B

FIGURE 2.9-13. Dermatomyositis. (A) Heliotrope rash; **(B)** Gottron papule. (Reproduced with permission from Dhoble A, Puttarajappa C, Neiberg A. Dermatomyositis and supraventricular tachycardia, Int Arch Med 2008 Nov 13;1(1):25.)

TABLE 2.9-8. Common Antibodies and Their Disease Associations

Antibody	Disease Association
ANA	SLE
Anti-CCP	RA
Anticentromere	CREST syndrome
Anti-dsDNA	SLE
Antihistone	Drug-induced SLE
Anti-Jo-1	Polymyositis/dermatomyositis
Antimitochondrial	Primary biliary cirrhosis
Anti-Scl-70	Systemic sclerosis
Anti-Sm	SLE
Anti–smooth muscle	Autoimmune hepatitis
Antitopoisomerase I	Systemic sclerosis
Anti-TSHR	Graves disease
c-ANCA	Vasculitis, especially Wegener
p-ANCA	Vasculitis, microscopic polyangiitis
RF	RA
U1RNP antibody	Mixed connective tissue disease

in a diffuse form involving the skin as well as the GI, GU, renal, pulmonary, and cardiovascular systems. Risk factors include female gender and age 35–50.

History/Pe

- Examination may reveal symmetric thickening of the skin of face and/or distal extremities.
  - **Limited cutaneous:** Head, neck, distal upper extremities.
  - **Diffuse cutaneous:** Torso, abdomen, proximal upper extremity/shoulder.
- **CREST syndrome:** Associated with limited cutaneous type.
- The diffuse form can lead to **GI dysmotility, pulmonary fibrosis,** cor pulmonale, **acute renal failure** (scleroderma renal crisis), and malignant hypertension.

Diagnosis

- Diagnosis and categorization depends on constellation of symptoms.
- RF and ANA may be ⊕.

MNEMONIC

CREST syndrome—

Calcinosis
Raynaud phenomenon
Esophageal dysmotility
Sclerodactyly
Telangiectasias

Q

A 49-year-old man presents with a painful, swollen big toe after a night of heavy drinking. His home medications are lansoprazole, ASA, sildenafil, and psyllium. Which medication should he temporarily discontinue?

- **Anticentromere antibodies** are specific for CREST syndrome (see Table 2.9-8).
- **Anti-Scl-70** (antitopoisomerase 1) **antibodies** are associated with diffuse disease and a poor prognosis (see Table 2.9-8).
- Eosinophilia may be seen.

Treatment

- Treatment is organ-based and includes frequent monitoring for progressive damage.
- Corticosteroids for acute flares (but ↑ risk of renal crisis); penicillamine can be used for skin changes.
- **Calcium channel blockers** for Raynaud phenomenon.
- **Angiotensin-converting enzyme inhibitors** for renal disease and for prevention/treatment of renal crisis.

Complications

Mortality is most commonly due to complications of pulmonary hypertension, as well as resulting renal or cardiac disease.

Systemic Lupus Erythematosus

A multisystem autoimmune disorder related to antibody-mediated cellular attack and deposition of antigen-antibody complexes. Black women are at highest risk. Usually affects women of childbearing age.

History/Pe

- Presents with nonspecific symptoms such as fever, anorexia, weight loss, and symmetric joint pain.
- The mnemonic **DOPAMINE RASH** summarizes the criteria for diagnosing SLE (see also Figure 2.9-14). Patients with four of the criteria are likely to have SLE (96% sensitive and specific).

Diagnosis

- A ⊕ ANA is highly sensitive but not specific. **Antibodies to dsDNA** and **Sm** are highly specific but not as sensitive (see Table 2.9-8).
  - **Drug-induced SLE:** ⊕ antihistone antibodies are seen in **100% of cases** but are nonspecific.
  - **Neonatal SLE:** Associated with ⊕ anti-Ro antibodies transmitted from mother to neonate.
- The following may also be seen:
  - Antiphospholipid antibodies.
  - Anemia, leukopenia, and/or thrombocytopenia.
  - Proteinuria and/or casts.

Treatment

- **NSAIDs** for mild joint symptoms.
- **Corticosteroids** for **acute exacerbations.**
- Corticosteroids, hydroxychloroquine, cyclophosphamide, and azathioprine can be used for progressive or refractory cases. A few have specific uses:
  - **Hydroxychloroquine:** Can be used for isolated skin and joint involvement.
  - **Cyclophosphamide:** Used for severe cases of lupus nephritis. Be sure to get a renal biopsy for patients with nephritic symptoms!

MNEMONIC

Criteria for SLE—

DOPAMINE RASH

Discoid rash
Oral ulcers
Photosensitivity
Arthritis (nondeforming)
Malar rash
Immunologic criteria: dsDNA, Sm proteins, anti-phospholipids
Neurologic symptoms (lupus cerebritis, seizures)
Elevated ESR
Renal disease
ANA ⊕
Serositis (pleural or pericardial effusion
Hematologic abnormalities



FIGURE 2.9-14. Systemic lupus erythematosus (SLE). The malar rash of SLE is a red-to-purple, continuous plaque extending across the bridge of the nose and to both cheeks. (Reproduced with permission from Bondi EE. Dermatology: Diagnosis and Therapy, 1st ed. Stamford, CT: Appleton & Lange; 1991.)

A

ASA (aspirin). This patient is having an acute gout attack, and ASA can cause ↓ excretion of uric acid by the kidney.

Giant Cell Arteritis

Formerly temporal arteritis; due to subacute granulomatous inflammation of the large vessels, including the aorta, external carotid (especially the **temporal** branch), and vertebral arteries. Risk factors include **polymyalgia rheumatica (affects almost half of patients),** age > 50 years, and female gender.

History/Pe

- Presents with new headache (unilateral or bilateral); scalp pain and **temporal tenderness;** and **jaw claudication.**
- Fever, permanent **monocular blindness,** weight loss, and myalgias and/or arthralgias (especially of the shoulders and hips) are also seen.

Diagnosis

- **ESR** > 50 mm/hr. (Influenced by age).
- Ophthalmologic evaluation.
- **Temporal artery biopsy: Definitive test.** Look for thrombosis; necrosis of the media; and lymphocytes, plasma cells, and giant cells.

Treatment

- Begin **high-dose prednisone** immediately to prevent ocular involvement (or involvement of the remaining eye after onset of monocular blindness). If suspected contribution to vision loss, give **pulse-dose steroids.**
- Obtain a biopsy, but do not delay treatment. Conduct a follow-up eye exam.

Complications

The most feared manifestation is blindness 2° to occlusion of the central retinal artery (a branch of the internal carotid artery) that may initially present as transient vision loss.

Complex Regional Pain Syndrome

A **pain syndrome** accompanied by **loss of function and autonomic dysfunction,** usually occurring after trauma. The disease has three phases: acute/traumatic → dystrophic phase → atrophic phase. Not linked with true nerve injury.

History/Pe

- **Diffuse pain occurs** out of proportion to the initial injury, often in a **non-anatomic** distribution.
- Pain can occur at any time relative to the initial injury.
- **Loss of function** of the affected limb is seen.
- **Sympathetic dysfunction** occurs and may be documented by skin, soft tissue, or blood flow changes.
- Skin temperature, hair growth, and nail growth may ↑ or ↓. Edema may be present.

Diagnosis

A clinical diagnosis, but objective evidence of changes in skin temperature, hair growth, or nail growth may be present.

KEY FACT

The lupus anticoagulant occurs in 5–10% of SLE cases. IgM or IgG binds proteins in clinical assay test and prolongs PTT.

KEY FACT

Libman-Sacks endocarditis: Noninfectious vegetations often seen on the mitral valve in association with SLE and antiphospholipid syndrome.

KEY FACT

SLE can cause a ⊕ VDRL or RPR test!

KEY FACT

SLE and RA both affect the MCP and PIP joints; the difference is that SLE is nondeforming.

Q

A 55-year-old woman presents to the clinic with a chief complaint of "blindness." She states that she experienced a temporary loss of vision in her left eye. She has also been experiencing new headaches and soreness in her jaw. Her vision exam is unremarkable. What diagnostic exam should be ordered?

Treatment

- Medications include NSAIDs, corticosteroids, low-dose tricyclic antidepressants, gabapentin, pregabalin, and calcitonin (no oral medications are consistently effective).
- Physical therapy modalities may be helpful.
- **Chemical sympathetic blockade** may relieve symptoms.
- Referral to a chronic pain specialist is appropriate for complicated cases.

Fibromyalgia

- A chronic pain disorder characterized by soft tissue and axial skeletal pain in the absence of joint pain. Inflammation is notably absent (see Table 2.9-9). May be difficult to distinguish from myofascial pain (< 11 painful areas).
- **Hx/PE:** Most common in **women 30–50 years of age;** associated with depression, anxiety, sleep disorders, inflammatory bowel syndrome, and cognitive disorders ("fibro fog").
- **Dx:** Multiple (≥ 11 of 18) painful areas over all four body quadrants and the axial skeleton must be present for diagnosis. The presence of < 11 of 18 painful areas or non-fibromyalgia-associated painful areas is known as **myofascial pain syndrome.**
- **Tx: Antidepressants** (a selective serotonin reuptake inhibitor/tricyclic antidepressant combination and two serotonin-norepinephrine reuptake inhibitors [SNRIs] have proven efficacy), gabapentin, pregabalin, muscle relaxants, and **physical therapy** (stretching, heat application, hydrotherapy). Avoid narcotics. Multidisciplinary patient education important.

Polymyalgia Rheumatica

An inflammatory rheumatic condition characterized by aching and stiffness in the shoulders, hips, and neck. Associated with **temporal arteritis.** Risk factors include female gender and age > 50 (see Table 2.9-9).

TABLE 2.9-9. Fibromyalgia vs Polymyalgia Rheumatica

Characteristic	Fibromyalgia	Polymyalgia rheumatica
Age and sex	Middle-aged women (30–50 years of age).	Women > 50 years of age.
Location	Various.	Shoulder and pelvic girdle.
ESR	Normal.	Markedly ↑ (> 100 mm/hr).
Muscle biopsy	Normal.	Normal.
Classic finding	Anxiety, stress, point tenderness, ⊖ workup.	Temporal arteritis; response to steroids.
Treatment	Antidepressants, NSAIDs, rest.	Low-dose prednisone.

A

Monocular amaurosis fugax is associated with giant cell (temporal) arteritis and may progress to complete vision loss. A temporal artery biopsy should be obtained.

- **Hx/PE:**
  - Presents with pain and stiffness of the **shoulder and pelvic girdle** musculature with difficulty getting out of a chair or lifting the arms above the head.
  - Other symptoms include **fever,** malaise, and weight loss. Weakness is generally not appreciated on exam.
- **Dx:** Labs reveal a markedly ↑ **ESR, often associated with anemia.**
- **Tx: Low-dose prednisone** (10–20 mg/day).

NOTES

HIGH-YIELD FACTS IN

NEUROLOGY

Clinical Neuroanatomy 258

Vascular Disorders 258
- Stroke 258
- Subarachnoid Hemorrhage 263
- Intracerebral Hemorrhage 263
- Subdural and Epidural Hematoma 264
- Cavernous Sinus Thrombosis 264

Headaches 266
- Common Primary Headaches 267
- Secondary Headaches 268

Seizure Disorders 268
- Status Epilepticus 270

Vertigo 271
- Benign Paroxysmal Positional Vertigo 271
- Acute Peripheral Vestibulopathy (Labyrinthitis or Vestibular Neuritis) 272
- Ménière disease 272

Syncope 273

Disorders of the Neuromuscular Junction 274
- Myasthenia Gravis 274
- Lambert-Eaton Myasthenic Syndrome 274
- Multiple Sclerosis 275
- Guillain-Barré Syndrome 276
- Amyotrophic Lateral Sclerosis 276

Dementia 277
- Alzheimer disease 277
- Vascular dementia 279
- Frontotemporal dementia (Pick disease) 279
- Normal Pressure Hydrocephalus 279
- creutzfeldt-Jakob disease 280
- Lewy Body dementia 281

Movement Disorders 282
- Huntington disease 282
- Parkinson disease 283

Neoplasms 283

Neurocutaneous Disorders 286
- Neurofibromatosis 286
- Tuberous Sclerosis 287

Aphasia 288
- Broca Aphasia 288
- Wernicke Aphasia 289

Coma 289

Nutritional Deficiencies 290

Ophthalmology 290
- Visual Field defects 290
- Glaucoma 291
- cataracts 292
- Age-Related Macular degeneration 293
- Retinal Vascular occlusion 294

Clinical Neuroanatomy

Tables 2.10-1 through 2.10-4 highlight critical aspects of clinical neuroanatomy, including the clinical presentation of common spinal cord lesions; facial nerve lesions; and pertinent clinical reflexes.

Vascular Disorders

STROKE

KEY FACT

Stroke is the fifth most common cause of death and a leading cause of major disability in the United States.

Disruption of cerebral blood flow leads to death of brain cells, resulting in acute onset of focal neurologic deficits. Can be ischemic (80%) or hemorrhagic (20%). Table 2.10-5 contrasts modifiable and nonmodifiable risk factors associated with stroke. Common etiologies are listed below.

- **Atherosclerosis** of the **extracranial** and **intracranial** vessels (internal/common carotid, basilar, and vertebral arteries).
- **Chronic hypertension, hypercholesterolemia,** or **diabetes** can damage perforating vessels supplying **deep** regions of brain, leading to **lacunar infarcts.**
- **Cardiac or aortic emboli.**
- **Other causes:** Hypercoagulable states, craniocervical dissection, venous sinus thrombosis, sickle cell anemia, vasculitis (eg, giant cell arteritis).

History/Pe

Symptoms are dependent on the vascular territory affected (see Table 2.10-6).

MNEMONIC

The 4 "deadly D's" of posterior circulation strokes—

Diplopia
Dizziness
Dysphagia
Dysarthria

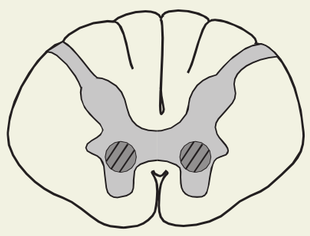
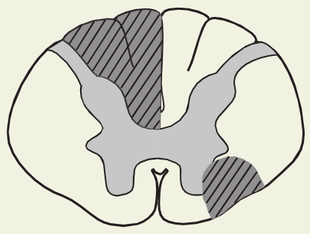
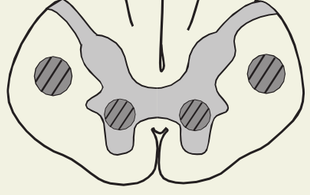
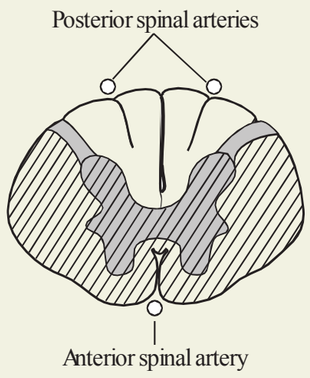
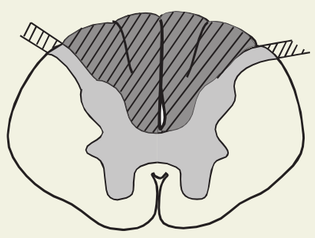
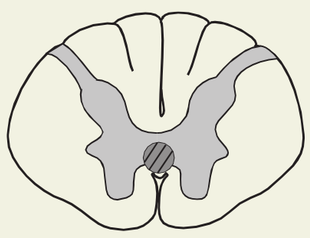
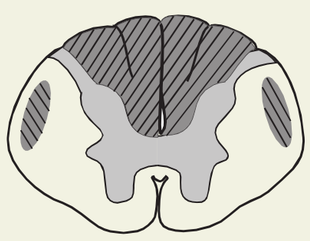
Diagnosis

- **Emergent head CT without contrast** (see Figure 2.10-1A) to differentiate ischemic from hemorrhagic stroke and identify potential candidates for **thrombolytic therapy. Ischemic strokes < 6 hours old** are usually **not visible on CT scan.** Labs to draw immediately, in case thrombolytic therapy or intervention may be required, include CBC, PT/PTT, cardiac enzymes and troponin, BUN/creatinine.
- **MRI** (see Figure 2.10-1B) to identify early ischemic changes not detected on CT.

TABLE 2.10-1. Spinal Tract Functions

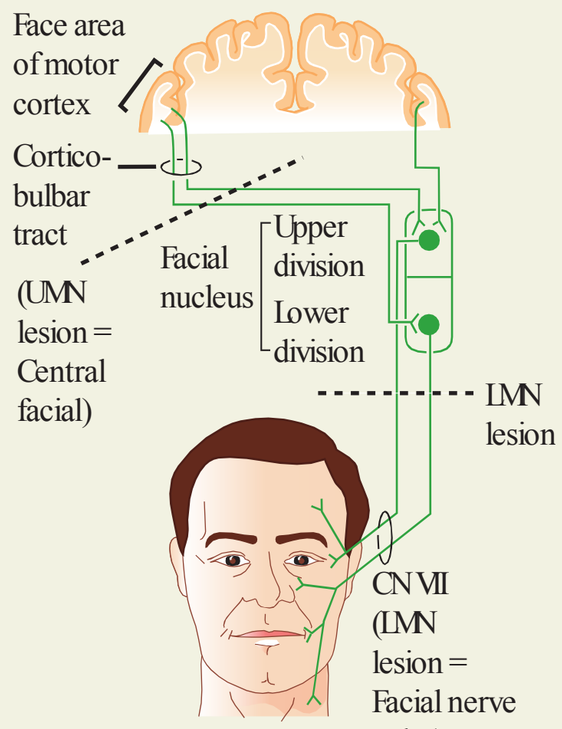
Tract	Function	Clinical Effects of Lesion
Lateral corticospinal	Movement of ipsilateral limbs and body.	Ipsilateral paresis at and below level of lesion.
Dorsal column medial lemniscus	Fine touch, vibration, conscious proprioception.	Ipsilateral loss of fine ouch, vibration, and proprioception at and below level of lesion.
Spinothalamic	Pain, temperature.	Contralateral loss of pain and temperature at and below level of lesion.

TABLE 2.10-2. Spinal Cord Lesions

Area affected	Disease	Characteristics
	Poliomyelitis and spinal muscular atrophy	LMN lesions only, due to destruction of anterior horns; flaccid paralysis.
	Multiple sclerosis	Due to demyelination; random and asymmetric lesions; mostly white matter of cervical region.
	Amyotrophic lateral sclerosis	Combined UMN and LMN deficits with no sensory or oculomotor deficits; both UMN and LMN signs. Commonly presents as fasciculations with eventual atrophy and weakness of hands; fatal. Riluzole treatment modestly ↑ survival by ↓ presynaptic glutamate release. Commonly known as Lou Gehrig disease in the United States and motor neuron disease in the United Kingdom. For Lou Gehrig disease, give rilouzole.
	Complete occlusion of anterior spinal artery	Spares dorsal columns.
	Tabes dorsalis	Caused by 3° syphilis. Results from degeneration (demyelination) of dorsal columns and roots → impaired sensation and proprioception, progressive sensory ataxia (inability to sense or feel the legs) → poor coordination. Associated with Charcot joints, shooting pain, Argyll Robertson pupils. Exam will demonstrate absence of DTRs and ⊕ Romberg sign.
	Syringomyelia	Syrinx (CSF-filled cavity within spinal cord) expands and damages anterior white commissure of spinothalamic tract. Can arise from trauma, tumors, and seen in 35% of Chiari malformations. Results in a capelike, bilateral loss of pain and temperature in upper extremities.
	Vitamin B_{12} deficiency	Subacute combined degeneration—demyelination of dorsal columns, lateral corticospinal tracts, and spinocerebellar tracts; ataxic gait, paresthesia, impaired position and vibration sense.

Adapted with permission from Le T et al. First Aid for the USMLE Step 1 2015. New York, NY: McGraw-Hill; 2015.

TABLE 2.10-3. Facial Nerve Lesions

Type	Description	Comments
UMN lesion	**Lesion of the motor cortex: Contralateral** paralysis of the **lower face only.**	**AL**exander **Bell** with **STD: A**IDS, **L**yme, **S**arcoid, **T**umors, **D**iabetes.
LMN lesion	Peripheral **ipsilateral** facial paralysis with inability to close the eye on the involved side. If it occurs idiopathically, it is Bell palsy. Gradual recovery is seen in most cases.	
Facial nerve palsy	Seen as a complication in **A**IDS, **L**yme disease, **S**arcoidosis, **T**umors, and **D**iabetes.	

Adapted with permission from Le T et al. First Aid for the USMLE Step 1 2015. New York, NY: McGraw-Hill; 2015.

MNEMONIC

MCA stroke can cause **CHANG**es—

Contralateral paresis and sensory loss in the face and arm
Hemiparesis
Aphasia (dominant)
Neglect (nondominant)
Gaze preference toward the side of the lesion

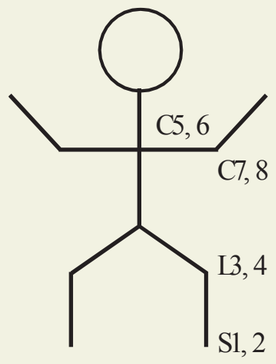
- Determine underlying cause of stroke:
  - Cardioembolic: **ECG; echocardiogram.**
  - Thrombotic: Carotid ultrasonography; MRA; CTA; transcranial Doppler; conventional angiography (see Figure 2.10-1C).
  - Other potential causes that should be worked up if there is a high index of suspicion: hypercoagulable states; sickle cell disease; vasculitis.

Treatment

Acute treatment measures are as follows:

- **Hemorrhagic stroke:** See the discussion of intracerebral hemorrhage.
- **Ischemic stroke:**
  - **Thrombolytics (tPA)** if it has been < **3 hours** since onset of stroke and there is no bleeding or absolute contraindications. Permissive hyper-

TABLE 2.10-4. Commonly Tested Reflexes

Distribution	Location	Comments
	Biceps = C5 nerve root. Triceps = C7 nerve root. Patella = L4 nerve root. Achilles = S1 nerve root. Babinski—dorsiflexion of the big toe and fanning of other toes; sign of UMN lesion, but normal reflex in the first year of life.	1–2, tie your shoes; 3–4, kick the door; 5–6, pick up sticks; 7–8, close the gate.

Adapted with permission from Le T et al. First Aid for the USMLE Step 1 2015. New York, NY: McGraw-Hill; 2015.

TABLE 2.10-5. Modifiable and Nonmodifiable Risk Factors for Stroke

Modifiable Risk Factors	Nonmodifiable Risk Factors
"Live the way a **COACH SHoulDD**":	**FAME:**
CAD	**F**amily history of MI or stroke
Obesity	**A**ge > 60
Atrial fibrillation (AF)	**M**ale gender
Carotid stenosis	**E**thnicity (black, Hispanic, Asian)
Hypercholesterolemia	
Smoking	
Hypertension	
Diabetes	
Drug use (cocaine, IV drugs)	

tension allowed in stroke for perfusion of ischemic area, but patient's systolic BP must be < 185 and diastolic BP < 110 mm Hg for tPA.
- **ASA** if it has been > 3 hours since onset of stroke. Consider switching to clopidogrel in patients who are already taking ASA.
- **Treat fever and hyperglycemia** as both are associated with worse prognoses in the setting of acute stroke.
- **Monitor** for signs and symptoms of brain swelling, ↑ ICP, and herniation. Treat acutely with **mannitol** and **hyperventilation.**
- **Prevent** and treat poststroke complications such as aspiration pneumonia, UTI, and DVT.

Preventive and long-term treatment measures:

- **Management of hypertension (single greatest risk factor for stroke), hypercholesterolemia,** and **diabetes.**
- **ASA** or **clopidogrel.**
- **Anticoagulation:** In new atrial fibrillation (AF) or hypercoagulable states,

TABLE 2.10-6. Common Stroke Symptoms by Vessel Territory

Artery	Distinguishing Symptoms
MCA	**Contralateral paresis** and **sensory loss** in the **face** and **arm;** gaze preference **toward** the side of the lesion. **Nondominant hemisphere—neglect.** **Dominant hemisphere—aphasia.**
ACA	**Contralateral paresis** and **sensory loss** in the **leg; cognitive** or **personality changes.**
PCA	Vertigo; homonymous hemianopsia.
Lacunar	Symptoms are pure motor, pure sensory, ataxic hemiparesis, or dysarthria.
TIA	Any of the symptoms above, depending on location of vascular lesion. **Neurologic deficit lasts < 24 hours (most last < 1 hour)** Often without findings on MRI

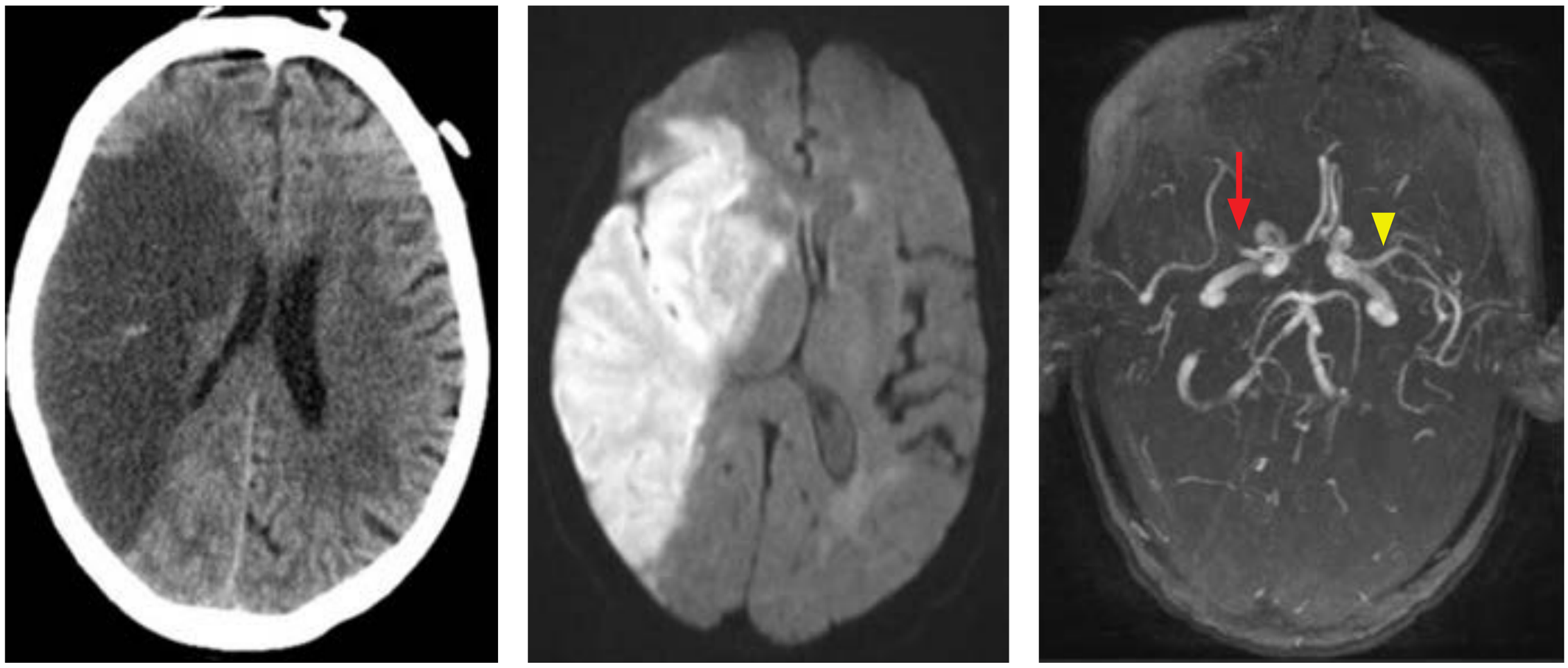
MNEMONIC

Contraindications to tPA therapy (major ones italicized)—

SAMPLE STAGES

Stroke or head trauma within the last 3 months
*__A__nticoagulation with INR > 1.7 or prolonged PTT
MI in past 3 months
Prior intracranial hemorrhage
Low platelet count (< 100,000/mm^3)
*__E__levated BP: Systolic > 185 or diastolic > 110 mm Hg
Major **S**urgery in the past 14 days
TIA (mild symptoms or rapid improvement of symptoms) within 6 months
GI or urinary bleeding in the past 21 days or **G**lucose < 50
*__E__levated (> 400 mg/dL) or ↓ (< 50 mg/dL) blood glucose
Seizures present at onset of stroke

*If values can be corrected using appropriate treatment prior to the 3-hour period, consider tPA treatment.

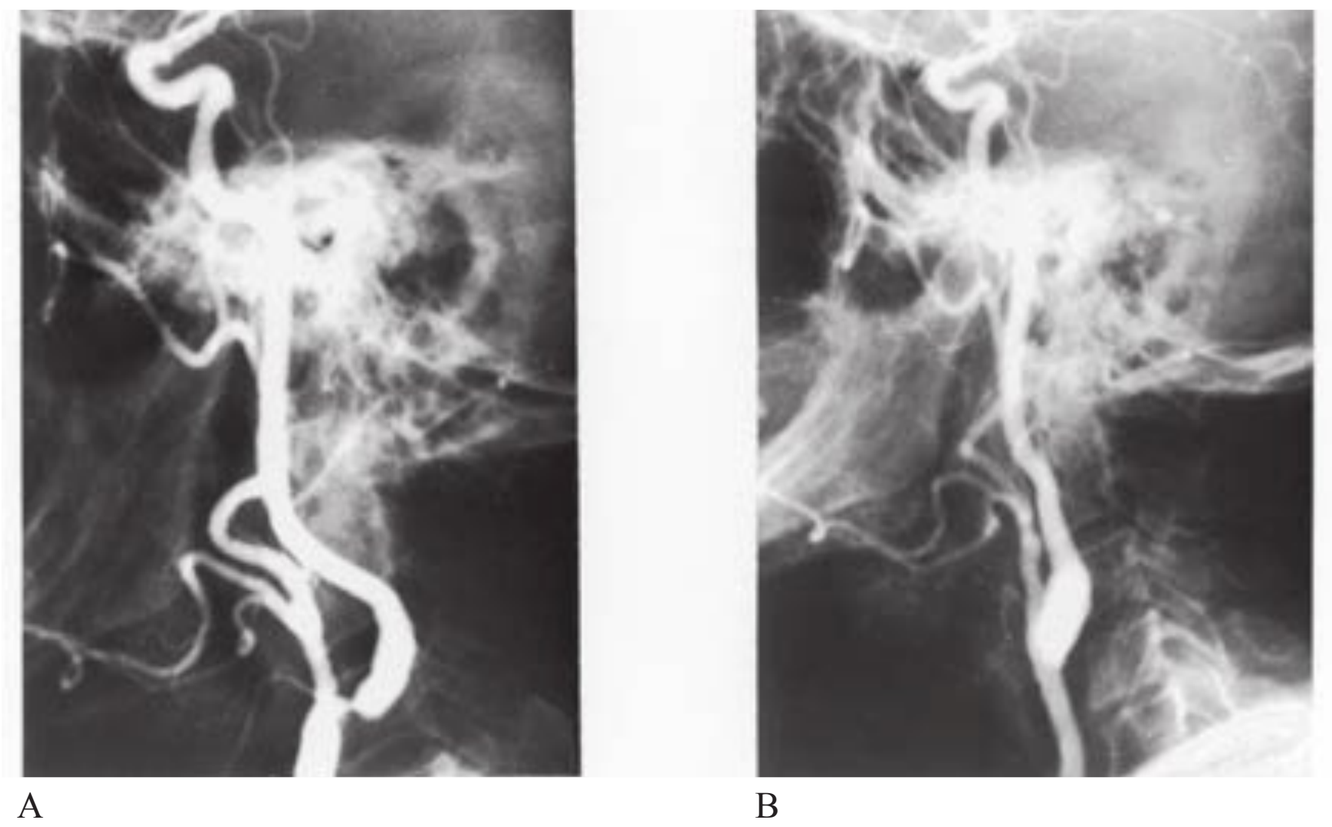


A B C

FIGURE 2.10-1. Acute ischemic stroke. Acute left hemiparesis in a 62-year-old woman. **(A)** Noncontrast head CT with loss of gray and white matter differentiation and asymmetrically decreased size of the right lateral ventricle in a right MCA distribution (indicating mass effect). **(B)** Diffusion-weighted MRI with reduced diffusion in the same distribution, consistent with an acute infarct; **diffusion-weighted sequences are the most sensitive modality for diagnosing an acute ischemic infarct. (C)** MRA shows the cause: an abrupt occlusion of the proximal right MCA (red arrow). Compare with the normal left MCA (yellow arrowhead). (Reproduced with permission from USMLE-Rx.com.)

the target INR is 2–3. In cases involving a prosthetic valve, the target INR is 2.5–3.5.

- **Carotid endarterectomy:** If stenosis is > 60% in symptomatic patients or > 70% in asymptomatic patients (contraindicated in 100% occlusion; see Figure 2.10-2).



A B

FIGURE 2.10-2. Vascular studies pre- and postendarterectomy. (A) Carotid arteriogram showing stenosis of the proximal internal carotid artery. **(B)** Postoperative arteriogram with restoration of the normal luminal size following endarterectomy. (Reproduced with permission from Way LW. Current Surgical Diagnosis & Treatment, 10th ed. Stamford, CT: Appleton & Lange; 1994.)

SUBARACHNOID HEMORRHAGE

Etiologies of SAH include **ruptured saccular aneurysms (berry aneurysms),** arteriovenous malformation (AVM), and **trauma** to the circle of Willis.

History/Pe

- Aneurysmal SAH presents with an **abrupt-onset, intensely painful "thunderclap" headache,** often followed by **neck stiffness** (due to meningeal irritation). Other signs of meningeal irritation, including photophobia, nausea/vomiting, and meningeal stretch signs (Kernig and Brudzinski signs), can also be seen.
- More than one-third of patients will give a history of a **"sentinel bleed"** ("warning leak") days to weeks prior to presentation.
- In the absence of neurosurgical intervention, rapid development of obstructive hydrocephalus or seizures often leads to ↓ arousal or frank coma and death.

Diagnosis

- Immediate head **CT without contrast** (see Figure 2.10-3A) to look for blood in the subarachnoid space.
- **LP if CT is** ⊖ to look for **RBCs, xanthochromia** (yellowish CSF due to breakdown of RBCs), ↑ protein (from the RBCs), and ↑ ICP.
- **Four-vessel angiography** (or equivalent noninvasive angiography such as CT angiography with 3D reconstructions) should be performed once SAH has been confirmed (see Figure 2.10-3B–D) to identify source of bleeding. Noninvasive angiography is warranted in high-risk cases and in those with high clinical suspicion even if CT and LP are unrevealing.

Treatment

- Neurosurgery for **definitive treatment!** May perform angiographic coiling and/or stenting to stabilize aneurysm.
- **Prevent rebleeding** (most likely to occur in the first 24 hours) by maintaining systolic BP < 150 mm Hg until the aneurysm has been clipped or coiled.
- **Prevent vasospasm and subsequent ischemic stroke** (most likely to occur 4–10 days after SAH) by administering calcium channel blockers (CCBs), such as **nimodipine.**
- Vasospasm is a **major** cause of **delayed morbidity and mortality** in patients with SAH.
- ↓ **ICP** by raising the head of the bed and instituting hyperventilation in an acute setting (< 30 minutes after onset).
- **Treat hydrocephalus** through a lumbar drain, serial LPs, or ventriculoperitoneal shunt.

INTRACEREBRAL HEMORRHAGE

- Bleeding within brain parenchyma. Commonly affects **deep brain regions** such as basal ganglia, thalamus, pons, and cerebellum. Some risk factors include hypertension, tumor, and illicit drug use.
  - Hypertension is the **most common** cause of intracerebral hemorrhage.

History/Pe

- **Early symptoms/signs: Focal motor or sensory deficits that often worsen as the hematoma expands.**
- **Late symptoms/signs:** Features of increased intracranial pressure (eg, vomiting and headache, bradycardia, reduced alertness).

KEY FACT

SAH = "the worst headache of my life" with **sudden** onset. Migraine = a gradually worsening headache (peak intensity > 30 minutes).

MNEMONIC

Conditions associated with berry aneurysms that can **MAKE** an **SAH** more likely—

Marfan syndrome
Aortic coarctation
Kidney disease (autosomal dominant, polycystic)
Ehlers-Danlos syndrome
Sickle cell anemia; **S**moking tobacco
Atherosclerosis
History (familial); **H**ypertension; **H**yperlipidemia

Q 1

A 68-year-old man presents to the ED with numbness and droop in right face, difficulty talking, as well as numbness and weakness in the right arm that began 2 hours ago. Where is this lesion, and what is the next best step in management?

Q 2

A 59-year-old man with prior medical history of polycystic kidney disease was admitted for treatment of SAH. Four days after admission, he developed weakness in his right arm. What could have prevented this?

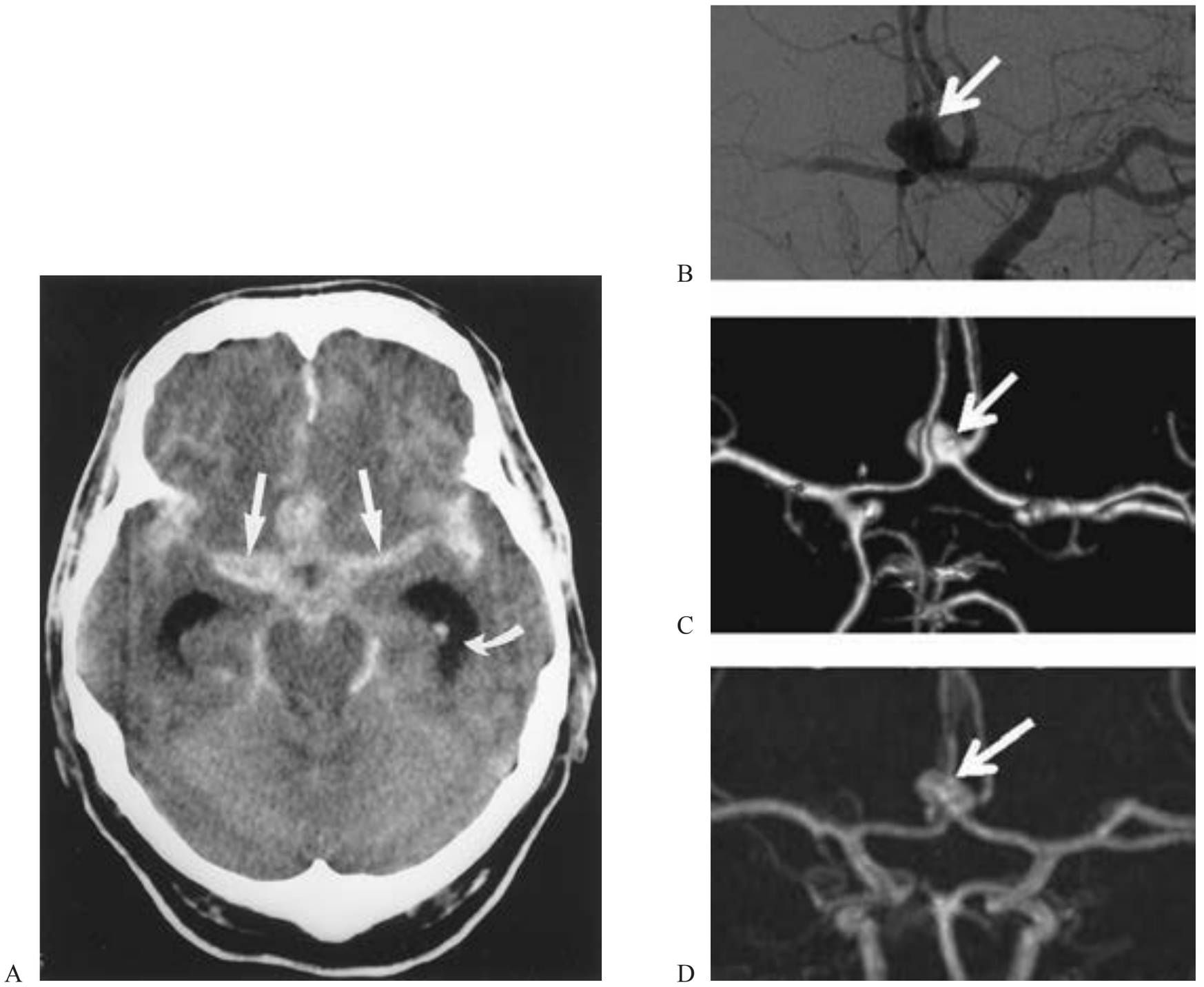


FIGURE 2.10-3. Subarachnoid hemorrhage. Noncontrast CT **(A)** showing SAH filling the basilar cisterns and sylvian fissures (straight arrows). The curved arrow shows the dilated temporal horns of the lateral ventricles/hydrocephalus. Coned-down images (right) from a catheter angiogram **(B),** a CT angiogram **(C),** and an MRA **(D)** show a saccular aneurysm arising from the anterior communicating artery (arrow).
(Part A reproduced with permission from Tintinalli JE et al. Tintinalli's Emergency Medicine: A Comprehensive Study Guide, 6th ed. New York, NY: McGraw-Hill; 2004. Parts B, C, D reproduced with permission from Doherty GM. Current Diagnosis & Treatment: Surgery, 13th ed. New York, NY: McGraw-Hill; 2010.)

1 **A**

Left MCA occlusion is the location, as aphasia and contralateral sensory loss and weakness are part of the description. CT of brain without contrast should be done to rule out hemorrhage and assess whether tPA should be initiated.

2 **A**

This patient's focal weakness is probably caused by ischemia secondary to vasospasm. It might have been prevented with administration of nimodipine, a CCB.

Diagnosis

Immediate noncontrast head CT (see Figure 2.10-4). Look for hyperdense areas, mass effect, or edema that may predict herniation.

Treatment

- Similar to that of SAH. Monitor for signs of herniation.
  - Suspect herniation if patient develops Cushing triad (hypertension, bradycardia, irregular respirations), fixed pupils, or loss of consciousness.
  - Herniation is a **medical emergency.** Treat with surgical evacuation of blood, removal of CSF, corticosteroids, or mannitol.

SUBDURAL AND EPIDURAL HEMATOMA

See Table 2.10-7 and Figure 2.10-5.

CAVERNOUS SINUS THROMBOSIS

A common etiology involves an uncontrolled infection of central facial skin, the orbit, or nasal sinuses that leads to **septic thrombosis** of the cavernous

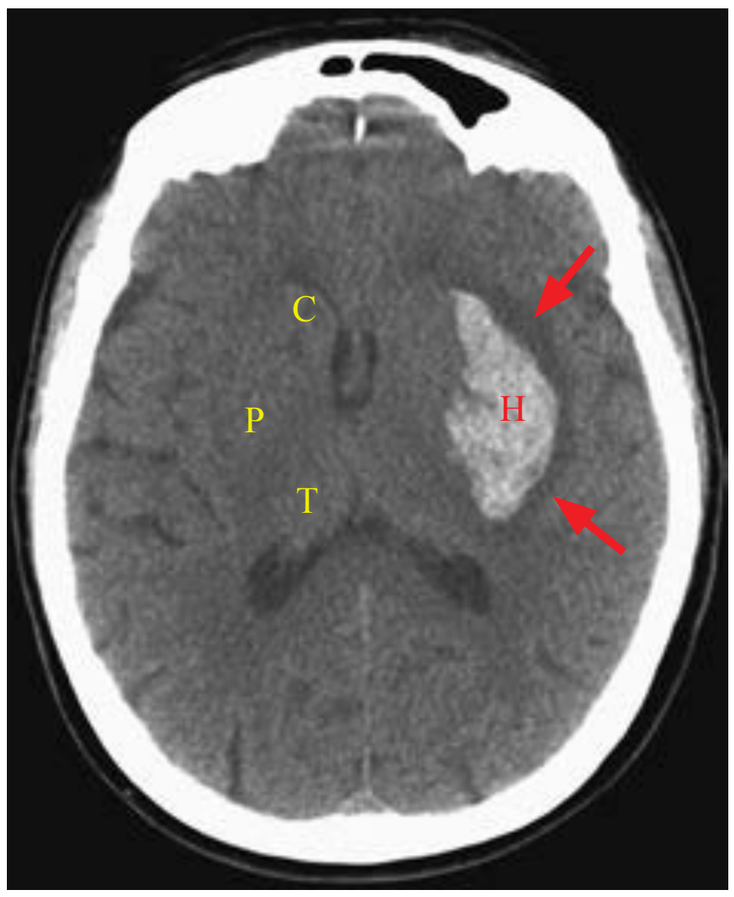


FIGURE 2.10-4. Intracerebral hemorrhage. Noncontrast head CT shows an intraparenchymal hemorrhage (H) and surrounding edema (arrows) centered in the left putamen, a common location for hypertensive hemorrhage. C, P, and T denote the normal contralateral caudate, putamen, and thalamus. (Reproduced with permission from Fauci AS et al. Harrison's Principles of Internal Medicine, 17th ed. New York, NY: McGraw-Hill; 2008.)

KEY FACT

A "blown pupil" suggests impending ipsilateral brainstem compression.

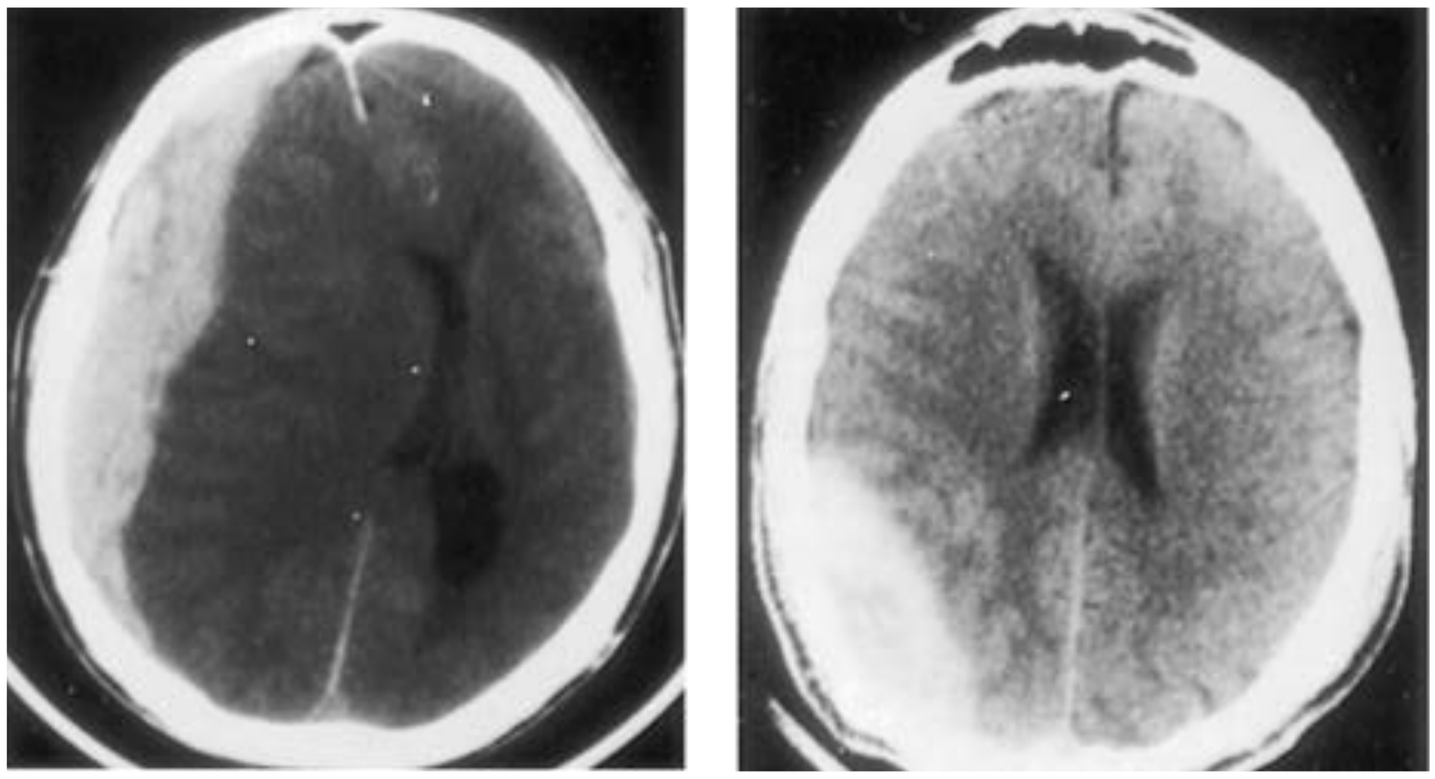
KEY FACT

Mental status changes associated with an expanding epidural hematoma occur within minutes to hours and classically include: acute loss of consciousness → lucid interval → gradual loss of consciousness. With a subdural hematoma, such changes can occur within days to weeks.

TABLE 2.10-7. Subdural Hematoma vs Epidural Hematoma

	Subdural	Epidural
Common etiology	Head trauma → rupture of **bridging veins** → accumulation of blood between dura and arachnoid membranes.	Head trauma → lateral skull fracture → tear of **middle meningeal artery** → accumulation of blood between skull and dura mater.
Epidemiology	Elderly, alcoholics.	Severe trauma.
Hx/PE	Headache; changes in mental status; contralateral hemiparesis; focal neurologic findings; mental status changes in elderly. Onset: subacute or chronic.	Immediate loss of consciousness followed by a lucid interval (minutes to hours).
Dx	CT findings **Crescent-shaped, concave hyperdensity acutely (isodense subacutely; hypodense chronically)** (see Figure 2.10-5A).	CT findings **Lens-shaped, biconvex hyperdensity** (see Figure 2.10-5B).
Tx	Neurosurgical evacuation **if symptomatic.** Subdural hematomas may **regress spontaneously.**	**Emergent neurosurgical evacuation.** Can quickly evolve to brain herniation and death 2° to the arterial source of bleeding.

Note: In the setting of mild traumatic brain injury without vomiting, headache, and loss of consciousness but normal head CT, observe for 4–6 hours. If observation period is unremarkable, the patient can be sent home with extensive return precautions.



A B

FIGURE 2.10-5. Subdural vs epidural hematoma. (A) Subdural hematoma. Note the crescent shape and the mass effect with midline shift. **(B) Epidural hematoma** with a classic biconvex lens shape. (Reproduced with permission from Aminoff MJ. Clinical Neurology, 3rd ed. Stamford, CT: Appleton &Lange; 1996.)

sinus. Staphylococcus aureus is the most common causative agent. Current antimicrobials have greatly ↓ both incidence and mortality.

History/Pe

- **Headache is the most common presenting symptom.**
- Patients may present with orbital pain, edema, visual disturbances (2° to oculomotor, abducens, or trochlear nerve involvement). On examination, they typically appear ill and have a **fever.**
- **Late findings:** Changes in mental status such as confusion, drowsiness, or coma suggest spread to the CNS or sepsis.

Diagnosis

- **MRI** (with gadolinium and MR venography) is main method for diagnosis but CT angiography and CT venography are also often used for diagnosis.
- Lab studies show ↑ WBC count.
- Blood cultures reveal the causative agent in up to 50% of cases.

Treatment

- Treat aggressively and empirically with broad-spectrum antibiotics:
  - **Penicillinase-resistant penicillin** (nafcillin or oxacillin) plus a **third- or fourth-generation cephalosporin** (eg, ceftriaxone or cefepime).
  - **Metronidazole** to cover anaerobic infection from sinus or dental sources.
  - **Vancomycin** can be added to address potential MRSA involvement.
  - Antifungal therapy is required for fungal cases.
- IV antibiotics are recommended for at least 3–4 weeks.
- Surgical drainage may be necessary if there is no response to antibiotics within 24 hours.

Headaches

Headaches can either be **primary/idiopathic** (ie, migraine, cluster, tension-type) or **secondary** (resulting from underlying disease, such as tumor or intracranial hemorrhage).

COMMON PRIMARY HEADACHES

Migraine Headache

Recurrent headache disorder with attacks that last 4–72 hours. Headache is typically unilateral, pulsating, moderate or severe intensity, aggravated by routine physical activity and can be associated with nausea, photophobia, phonophobia, and aura (reversible focal neurologic symptoms). Affects **women** more often than men; often familial; onset is usually by the **early 20s.** Linked to changes in **vascular tone** and neurotransmitters (**serotonin,** dopamine). **Triggers** include certain foods (eg, red wine), fasting, stress, menses, OCPs, bright light, and disruptions in normal sleep patterns.

History/Pe

- Presents with a throbbing headache (> 2 hours but usually < 24 hours) that is associated with **nausea, vomiting, photophobia,** and **noise sensitivity.** Headache is usually relieved by **sleep and darkness.** Migraine can be with or without **aura.**
  - **Classic presentation of migraine with aura: Unilateral pulsating HA,** preceded by a visual **aura** in the form of either scintillating scotomas (bright or flashing lights) or visual field cuts.

Diagnosis

Based on the history and an otherwise ⊖ workup.

Treatment

- **Avoid known triggers.**
- **Abortive therapy** includes **triptans** (after OTC NSAIDs have failed), alone or in addition to other analgesics such as naproxen. Consider symptomatic treatment for nausea.
- **Prophylaxis** for frequent or severe migraines includes **anticonvulsants** (eg, gabapentin, topiramate), **TCAs** (eg, amitriptyline), **β-blockers** (propranolol), and **CCBs.**

Cluster Headache

Men are affected more often than women; average age of onset is 25.

History/Pe

- Presents as a brief, **excruciating, unilateral periorbital headache** that lasts 30 minutes to 3 hours, during which time the patient tends to be extremely restless.
- Attacks tend to occur in **clusters,** affecting the same part of the head at the same time of day (commonly during sleep) during a certain season of the year.
- Associated symptoms include **ipsilateral lacrimation** of the eye, conjunctival injection, Horner syndrome, and nasal stuffiness.

Diagnosis

- Classic presentations with a history of **repeated attacks** over an extended period of time **do not need imaging. First episodes** require a workup (ie, MRI, carotid artery ultrasound) to exclude structural brain lesion or disorders associated with Horner syndrome (ie, carotid artery dissection, cavernous sinus infection).

KEY FACT

If a 25-year-old man wakes up repeatedly during the night with unilateral periorbital pain associated with ipsilateral lacrimation, think cluster headache.

KEY FACT

If a 30-year-old woman complains of headaches at the end of the day that worsen with stress and improve with relaxation or massage, think tension-type headache.

Q 1

A 28-year-old woman with no prior medical history presents with throbbing, unilateral headache that is exacerbated by menstruation and minimally relieved by acetaminophen and lying in a dark room. She would like something that would provide more symptomatic relief. What abortive therapy would you prescribe?

Q 2

A 24-year-old woman with a BMI of 33 presents with a 3-week history of constant retro-orbital headache with occasional nausea, vomiting, and tinnitus. She also developed new-onset diplopia 2 hours prior to presentation. On physical exam, she is noted to have papilledema. What is the most likely diagnosis, and what are the risk factors for this condition?

Treatment

- **Acute therapy:** High-flow O_2 or sumatriptan injection.
- **Prophylactic therapy: Verapamil** is first line. Alternatives include lithium, valproic acid, and topiramate.

Tension-Type Headache

History/Pe

Presents with **tight, bandlike pain** that is triggered by fatigue or stress. Nonspecific symptoms (eg, anxiety, poor concentration, difficulty sleeping) may also be seen. Usually occurs at the end of the day.

KEY FACT

Tension-type headaches are the most common type of headache diagnosed in adults.

Diagnosis

Must have at least two of the following characteristics: bilateral location, pressing/tightening quality; mild-moderate intensity; not aggravated by routine physical activity. Rule out giant cell arteritis in patients > 50 years of age with new headaches by obtaining an ESR, even if headaches are mild with no associated constitutional or vascular symptoms.

Treatment

Relaxation, massage, hot baths, and **avoidance of exacerbating factors. NSAIDs** and **acetaminophen** are first-line abortive therapy, but triptans can also be considered.

KEY FACT

Headache red flags Sudden onset of most severe headache ever, neurologic sequelae, nocturnal headache, morning vomiting, onset of headache after 50 years of age, focal neurologic signs or symptoms, papilledema, headache subsequent to head trauma.

SECONDARY HEADACHES

Consider secondary headaches when "red flags" are present.

History/Pe

- Significant findings include **fever or rash** (consider meningitis or other infectious causes), **jaw claudication** (specific for temporal arteritis), or constitutional symptoms such as **weight loss** (associated with neoplastic, inflammatory, or infectious conditions).
- **Photophobia, nausea, vomiting, and neck stiffness** can be associated with aneurysmal SAH and meningitis due to meningeal irritation.
- Conduct full general and neurologic exams, including a **funduscopic** exam.
- **Neurologic sequelae:** Look for **diplopia,** mental status changes or associated symptoms (numbness, weakness, dizziness, ataxia, visual disturbances), **papilledema,** or pupillary abnormalities (partial CN III palsy or Horner syndrome).

Diagnosis

- **If SAH is suspected,** obtain a **head CT without contrast.**
- Obtain a CBC to rule out systemic infections.
- If temporal arteritis is suspected, obtain an ESR.

Treatment

- Directed toward underlying cause of headaches.
- Analgesics for pain relief.

1 A

This patient's symptoms are consistent with migraine headaches. You would prescribe sumatriptan for abortive therapy.

2 A

Given this patient's symptoms and risk factors, she probably has pseudotumor cerebri, also known as idiopathic intracranial hypertension (IIH). In IIH, symptoms are suggestive of a brain tumor and CSF pressure will be elevated; however, neuroimaging will be normal. Obesity, tetracycline, growth hormone, and excess vitamin A are risk factors for the disease.

Seizure Disorders

Sudden changes in neurologic activity caused by abnormal electrical activity in the brain that can often be detected on EEG. See Table 2.10-8 for com-

TABLE 2.10-8. Causes of Seizure by Age Group

Infants	Children (2–10 years)	Adolescents	Adults (18–35 years)	Adults (> 35 years)
Perinatal injury	Idiopathic	Idiopathic	Trauma	Trauma
Infection	Infection	Trauma	Alcoholism	Stroke
Metabolic	Trauma	Drug withdrawal	Brain tumor	Metabolic disorders
Congenital	Febrile	AVM		Alcoholism
				Brain tumor

mon etiologies by age. Etiologies of seizures, and their distinguishing features, include the following:

- Idiopathic epilepsy (recurrent, unprovoked seizures): May be due to genetics, developmental factors, early life brain injuries, etc.
- Acquired epilepsy could be caused by the following:
  - Structural brain lesion (tumor, stroke, AVM hemorrhage, or developmental abnormality). Tend to have **focal** onset or focal postictal deficit, suggesting **focal CNS pathology.**
  - Non-neurologic etiologies: **Hypoglycemia, hyponatremia, hypocalcemia, hyperosmolar states, hepatic encephalopathy,** uremia, porphyria, **drug overdose** (cocaine, antidepressants, neuroleptics, methylxanthines, lidocaine), **drug withdrawal** (alcohol and other sedatives), eclampsia, hyperthermia, hypertensive encephalopathy, head trauma, and cerebral hypoperfusion.

History/Pe

Hx should be focused to determine whether seizure is **partial, generalized,** or **unknown.** Status epilepticus will be discussed in a separate section.

- **Partial:** Abnormal electrical activity arises from a **discrete region (or multiple discrete regions) of the brain.** Can involve motor features as well as sensory, autonomic, or psychic features (eg, fear, déjà vu, hallucinations). **Aura** is common (auditory, visual, olfactory, or tactile hallucinations). A postictal focal neurologic deficit (eg, **hemiplegia/hemiparesis,** or **Todd paralysis**) is possible and usually resolves within 24 hours. Can be **simple** or **complex.**
  - **Simple: No impaired level of consciousness.**
  - **Complex:** Typically involve the **temporal lobe** (70–80%) with bilateral spread of the aberrant electrical discharge, **leading to impaired level of consciousness.** Postictal confusion/disorientation/amnesia are characteristic.
- **Generalized seizures:** Seizure activity that involves **both cerebral hemispheres** resulting in **impaired level of consciousness.** Examples include tonic-clonic, absence, myoclonic, clonic, tonic, and atonic. Tonic-clonic and absence are discussed below.
  - **Tonic-clonic: Sudden loss of consciousness** with extension of the back and contraction of muscles (chest and extremities), repetitive, symmetric clonic (alternation between muscle contraction and relaxation) movements. Etiology often idiopathic. Simple and complex partial seizures may evolve into secondary generalized tonic-clonic seizures.
    - Marked by **incontinence** and **tongue biting.**
    - Patients may appear **cyanotic** during the ictal period.
    - Postictal confusion and drowsiness. Muscle aches and headaches may also be present.

KEY FACT

If a patient presents with uncontrollable twitching of his thumb and is fully aware of his symptoms, think simple partial seizures.

KEY FACT

Both simple partial and complex partial seizures may evolve into 2° generalized seizures.

KEY FACT

If a patient presents with an episode of lip smacking associated with an impaired level of consciousness and followed by confusion, think complex partial seizures.

Q

A 40-year-old man presents to the ED with a single simple partial seizure of 1 minute but is no longer symptomatic. He also complains of 2 months of morning headaches and one episode of vomiting in the past week. What is the next step in management?

- **Childhood absence epilepsy:** Presents with **brief (5- to 10-second),** often unnoticeable episodes of **impaired consciousness** (petit mal seizures) occurring up to hundreds of times per day. Can appear to be **daydreaming** or **staring.** Symptoms may include sudden stop in motion, lip smacking, eyelid flutter, and chewing motions. Can be triggered by hyperventilation. **No postictal phase.** Begin in **childhood;** subsides before adulthood. Often **familial.**

Diagnosis

- Hx/PE.
- Obtain an **EEG.**
  - **Partial seizures:** Look for epileptogenic focus.
  - **Childhood absence epilepsy:** EEG shows 3-per-second spike-and-wave discharges (remember classic EEG findings, but do **not** worry about learning how to read them!). EEG changes can be triggered by **hyperventilation.**
  - **Tonic-clonic:** EEG typically shows 10-Hz activity during the tonic phase and slow waves during the clonic phase.
  - If EEG is normal during event concerning for seizure, think of **pseudoseizures.**
- Serum prolactin levels may be elevated in the immediate postictal period of generalized and complex-partial seizures.
- Rule out systemic causes with a CBC, electrolytes, calcium, fasting glucose, LFTs, a renal panel, RPR, ESR, and a toxicology screen.
- A focal seizure implies a focal brain lesion. Evaluate by CT or MRI with contrast.

KEY FACT

If a patient presents with clonic movements associated with loss of consciousness and incontinence, think tonic-clonic (grand mal) seizures.

KEY FACT

If a child is brought from school to her pediatrician after experiencing multiple intermittent 5-second episodes of staring into space, think childhood absence epilepsy.

KEY FACT

Petit mal seizures may be described with the classic EEG finding of 3-per-second spike-and-wave discharges.

Treatment

- **Secure airway** when appropriate.
- For acute seizures lasting **longer than 5 minutes, see treatment of status epilepticus below.**
- In cases of systemic 2° seizures, **treat the underlying cause.**
- For **partial** and **tonic-clonic** seizures, levetiracetam (Keppra), phenytoin, carbamazepine (Tegretol), phenobarbital, and valproic acid have similar efficacy and can be used as chronic monotherapy.
  - In **children, phenobarbital** is the first-line anticonvulsant.
  - If a certain antiepileptic is ineffective as monotherapy, try an alternative. If alternative is ineffective, try a regimen of multiple antiepileptics.
  - Other treatment options include gabapentin, topiramate, and oxcarbazepine.
- **Absence seizures: First line is ethosuximide;** second line is **valproic acid.**
- **Intractable temporal lobe seizures:** Consider **anterior temporal lobectomy.**
- Treatment is not necessary for a single episode of seizure.

A

Order CT of brain because history is suggestive of brain tumor and patient is no longer symptomatic. If seizures recur, consider beginning anticonvulsant therapy.

STATUS EPILEPTICUS

A **medical emergency** consisting of prolonged seizures (traditionally defined as > **30 minutes, recent sources use > 5 minutes**) or two or more seizures that occur without a return to baseline consciousness within 30 minutes.

- Common causes include anticonvulsant withdrawal/noncompliance, anoxic brain injury, EtOH/sedative withdrawal or other drug intoxication, metabolic disturbances (eg, hyponatremia), head trauma, and infection.
- Mortality is 10–20%.

Diagnosis

- Treatment and diagnostic workup should be initiated simultaneously.
- Determine the underlying cause with collateral history, physical exam, CBC, electrolytes, calcium, glucose, ABGs, LFTs, BUN/creatinine, ESR, antiepileptic drug levels, and a toxicology screen.
- **Continuous EEG monitoring if nonconvulsive status epilepticus is suspected or if patient is not waking up after clinically obvious seizures stop.**
- If intracranial pathology is suspected, obtain a stat head CT.
- Obtain an LP in the setting of fever or meningeal signs, but only after a CT scan has been obtained to assess the safety of the LP.

Treatment

- Maintain **airway, breathing, circulation (ABCs);** consider rapid intubation for airway protection.
- To rapidly treat potential etiologies, administer **thiamine, followed by glucose and naloxone.**
- SE treatment strategies vary greatly among different institutions. Following is an example guide:
  - Give an **IV benzodiazepine** (lorazepam or diazepam) within 0–5 minutes.
  - Give another dose of IV benzodiazepine at 5–10 minutes.
  - If patient is still seizing at 20 minutes, give **fosphenytoin,** valproate sodium, phenobarbital, levetiracetam, or continuous infusion of midazolam.
  - For refractory status epilepticus (RSE), give continuous antiepileptic drugs (AEDs) with bolus for breakthrough SE. Early intubation is advisable when giving continuous AEDs.

KEY FACT

Though status epilepticus is traditionally defined as seizures lasting > 30 minutes, treatment should begin for any seizure lasting > 5 minutes to prevent cortical necrosis from excitatory toxicity.

KEY FACT

Withdrawal from **ABBA** can cause seizures:
Alcohol
Benzodiazepines
Barbiturates
Anticonvulsants

Vertigo

Before discussing conditions that cause vertigo, it is worth defining **vertigo** and differentiating it from **lightheadedness.** Many times, **"dizziness"** is used to describe vertigo and lightheadedness. **Vertigo** is feeling like **you or your surroundings are moving,** though in actuality there is **no movement,** while **lightheadedness** is when one complains that they are about to **faint** or **"pass out."**

BENIGN PAROXYSMAL POSITIONAL VERTIGO

A common cause of recurrent **peripheral vertigo** resulting from an **otolith** ("earstone") that leads to disturbances in the semicircular canals.

History/Pe

Patients present with **transient, episodic vertigo (lasting < 1 minute)** and **nystagmus triggered by changes in head position** (eg, while turning in bed, getting in and out of bed, or reaching overhead). Patients may complain of vertiginous or nonvertiginous dizziness or lightheadedness.

Diagnosis

- **Dix-Hallpike maneuver:** Have the patient turn his or her head 45 degrees right or left and go from a sitting to a supine position. If vertigo and the typical nystagmus (upbeat and toward the affected side) are reproduced, BPPV is the likely diagnosis.
- Nystagmus that persists for > 1 minute, gait disturbance, or vomiting should raise concern for a central lesion.

Treatment

- Eighty percent of cases can be resolved with a modified Epley maneuver (an extended version of the Dix Hallpike maneuver used as treatment).
- The condition usually subsides spontaneously in weeks to months, but 30% recur within a year. Antivertigo medications (eg, meclizine) are generally contraindicated, as they have limited efficacy, they are sedating, and they inhibit vestibular compensation, which may lead to chronic unsteadiness.

ACUTE PERIPHERAL VESTIBULOPATHY (LABYRINTHITIS OR VESTIBULAR NEURITIS)

History/Pe

- Presents with **acute onset of severe vertigo, head motion intolerance, and gait unsteadiness** accompanied by **nausea, vomiting, and nystagmus.**
- **Labyrinthitis:** Auditory or aural symptoms (tinnitus, ear fullness, or hearing loss). Lateral pontine/cerebellar stroke (anterior inferior cerebellar artery territory) may present with similar symptoms.
- **Vestibular neuritis:** Lacks auditory or aural symptoms. Lateral medullary/cerebellar stroke (posterior inferior cerebellar artery territory) can present with similar symptoms.

KEY FACT

If you see someone with vertigo and vomiting for 1 week after having been diagnosed with a viral infection, think acute vestibular neuritis.

Diagnosis

- A **diagnosis of exclusion** once the more serious causes of vertigo (eg, cerebellar stroke) have been ruled out.
  - Acute peripheral vestibulopathy demonstrates the following:
    - An abnormal vestibulo-ocular reflex as determined by a bedside head impulse test (ie, rapid head rotation from lateral to center while staring at the examiner's nose).
    - A predominantly horizontal nystagmus that always beats in one direction, opposite the lesion.
    - No vertical eye misalignment by alternate cover testing.
  - If patients are "high risk"—ie, if they have atypical eye findings or neurologic symptoms or signs, cannot stand independently, have head or neck pain, are > 50 years of age, or have one or more stroke risk factors—MRI with diffusion-weighted imaging is indicated.

Treatment

Acute treatment consists of corticosteroids given < 72 hours after symptom onset and antivertigo agents (eg, meclizine). The condition usually subsides spontaneously within weeks to months.

MÉNIÈRE DISEASE

A cause of recurrent **vertigo with auditory symptoms** that affects at least 1 in 500 in the United States. More common among women.

History/Pe

Presents with **recurrent episodes of severe vertigo, hearing loss, tinnitus,** and **ear fullness,** often lasting hours to days. **Nausea and vomiting are typical.** Patients progressively **lose low-frequency** hearing over years and may become deaf on the affected side.

Diagnosis

The diagnosis is made clinically and is based on a thorough history and physical. **Two episodes** lasting ≥ 20 minutes with remission of symptoms between episodes, hearing loss documented at least once with audiometry, and tinnitus or aural fullness are needed to make the diagnosis once other causes (eg, TIA, otosyphilis) have been ruled out.

Treatment

- **Acute:** Meclizine or benzodiazepines to control spinning sensation during acute attacks; antiemetics for nausea/vomiting.
- **Chronic:** Dietary changes that limit salt intake to avoid fluid retention; diuretics.
- For severe unilateral cases, intratympanic injection of gentamicin into the middle ear (absorbed by the inner ear) has been shown to reduce the frequency and severity of vertigo attacks.

Syncope

One of the **most common causes** of loss of consciousness **2° to a sudden drop in cerebral perfusion.** Etiologies can be **cardiac** or **noncardiac.** Presyncope can be associated with noncardiac causes and is described as a feeling of imminent loss of consciousness without actual fainting. Commonly **confused with seizures.**

History/Pe

- Patients may report a **trigger** (eg, orthostatics, standing for a long period of time, fear/sight of blood, Valsalva maneuver).
- **Noncardiac:** Typically involves prodromal symptoms that lead to loss of consciousness and muscle tone for < 30 seconds and recovery within seconds. Screen for the following potential etiologies:
  - **Orthostatic hypotension:** Symptoms triggered by postural changes. Common causes include dehydration and autonomic neuropathy (commonly seen in patients with diabetes).
  - **Vasovagal:** Sudden increase in vagal tone triggered by prolonged standing, emotional distress, painful stimuli. Patient may experience prodromal symptoms of nausea, warmth and diaphoresis prior to syncope.
- **Cardiac:** Does not typically involve prodromal/postdromal symptoms; patient may have history of arrhythmia, valvular disease, structural heart disease. Screen for the following potential etiologies:
  - **Left ventricular outflow tract obstruction (LVOTO)** (eg, **aortic stenosis, hypertrophic obstructive cardiomyopathy**); syncope with exertion or during exercise.
  - **Arrhythmia:** History of CAD, MI, cardiomyopathy, Wolff-Parkinson-White syndrome, or reduced EF.
  - **Torsades de pointes:** Triggered by electrolyte abnormalities (K^+; Mg^+) or any medications that can prolong QT interval.

Diagnosis

- Unless there is a clear vasovagal syncope in a young patient with no history of cardiac disease or risk factors, place all patients on **telemetry** or **Holter monitoring** to evaluate for **arrhythmia,** and rule out **myocardial ischemia** with an **ECG** and **cardiac enzymes.**

- Consider an **echocardiogram,** a **tilt-table test,** or **neuroimaging,** especially vascular.
- Consider seizure and rule out with EEG if:
  - Patient experiences limb jerking that is unilateral or lasts > 30 seconds.
  - Patient has prolonged confusion after the episode.
  - Patient bites the lateral aspect of his or her tongue.

Treatment

Treat the underlying cause; avoid triggers.

Disorders of the Neuromuscular Junction

MYASTHENIA GRAVIS

An **autoimmune disorder** caused by antibodies that bind to **postsynaptic acetylcholine (ACh) receptors** located at the neuromuscular junction. Most often affects young adult women, and can be associated with **thymoma, thyrotoxicosis,** and other autoimmune disorders.

History/Pe

- Presents with fluctuating **ptosis or double vision,** bulbar symptoms (eg, dysarthria, dysphagia), and **proximal muscle weakness. Symptoms typically worsen at the end of the day.**
- Patients may report difficulty in: climbing stairs, rising from a chair, brushing hair, and swallowing.
- **Myasthenic crisis** is rare but includes the potentially lethal complications of respiratory compromise and aspiration.

Diagnosis

- Best initial diagnostic test is acetylcholine receptor antibody. Edrophonium (Tensilon test) is an anticholinesterase that can be used as a diagnostic tool because it rapidly reverses symptoms.
- An abnormal **single-fiber EMG** and/or a **decremental response to repetitive nerve stimulation** can yield additional confirmation.
- **Chest CT** is used to evaluate for thymoma.

Treatment

- Anticholinesterases **(pyridostigmine)** are used for symptomatic treatment.
- **Prednisone,** other immunosuppressants (eg, azathioprine, cyclosporine, mycophenolate mofetil), plasmapheresis, or IVIG can also be used for treatment.
- **Resection of thymoma** can be curative.
- **Avoid giving certain antibiotics** (eg, aminoglycosides, fluoroquinolones) **and drugs** (eg, β-blockers) to patients with myasthenia gravis because of their direct/indirect effects on the neuromuscular junction.

LAMBERT-EATON MYASTHENIC SYNDROME

- A **paraneoplastic** autoimmune disorder caused by antibodies directed toward presynaptic calcium channels in the neuromuscular junction. **Small cell lung carcinoma** is a significant risk factor (60% of cases).

History/PE

Presents with weakness of proximal muscles along with depressed or absent deep tendon reflexes. **Extraocular, respiratory,** and **bulbar** muscles are typically **spared.** Weakness will improve with ↑ activity.

Diagnosis

Repetitive nerve stimulation reveals a characteristic incremental response. Also diagnosed by autoantibodies to presynaptic calcium channels and a chest CT indicative of a lung neoplasm.

KEY FACT

Repetitive nerve stimulation reveals a characteristic incremental response in Lambert-Eaton myasthenic syndrome but shows a decremental response in myasthenia gravis.

Treatment

- Treat small cell lung carcinoma; tumor resection may reverse symptoms.
- 3,4-diaminopyridine or guanidine can be given; acetylcholinesterase inhibitors (eg, pyridostigmine) can be added to either regimen.
- Corticosteroids and azathioprine can be combined or used alone for immunosuppression in cases where a neoplasm cannot be identified and an autoimmune cause is suspected.

MULTIPLE SCLEROSIS

Autoimmune disorder of unclear etiology, but thought to be **T-cell mediated.** The female-to-male ratio is 3:2, and onset is typically between 20 and 40 years of age. MS becomes more common with increasing distance from the equator during childhood. Subtypes are **relapsing-remitting** (most common), 1° progressive, 2° progressive, and progressive relapsing.

History/PE

- Presents with **multiple neurologic complaints that are separate in time and space and are not explained by a single lesion.** As the disease progresses, permanent deficits can accumulate.
- Limb weakness, gait unsteadiness, paresthesias, **optic neuritis, ophthalmoplegia,** diplopia, vertigo, nystagmus, urinary retention, sexual and bowel dysfunction, depression, and cognitive impairment are also seen. Symptoms classically worsen transiently with hot showers.
- Attacks are unpredictable but on average occur every 1.5 years, lasting for 2–8 weeks.
- Neurologic symptoms can come and go or be progressive. Those with a **relapsing and remitting history** have the **best prognosis.**

KEY FACT

The classic triad (Charcot's triad) in MS is scanning speech, intranuclear ophthalmoplegia, and nystagmus.

KEY FACT

Pregnancy may be associated with a ↓ in MS symptoms.

Diagnosis

When clinical evidence alone is not sufficient, use MRI and LP as outlined by McDonald Diagnostic Criteria for definitive diagnosis.

- MRI (diagnostic test of choice for MS) shows **multiple, asymmetric,** often **periventricular** white matter lesions (Dawson fingers), especially in the **corpus callosum.** Active lesions enhance with gadolinium.
- CSF reveals ↑ IgG index, or at least two oligoclonal bands not found in the serum (nonspecific).

KEY FACT

For optic neuritis, give IV, not oral, corticosteroids.

Treatment

- Acute exacerbations: High-dose, IV **corticosteroids. Plasma exchange** in patients who do not respond to corticosteroids.
- Disease modifying medications: **Immunomodulators** for relapsing-remitting MS can decrease number of relapses. Treat with "ABCs": Interferon-β_{1a} (**A**vonex/Rebif), interferon-β_{1b} (**B**etaseron), and copolymer-1 (**C**opaxone).

- **Symptomatic therapy** is crucial and includes baclofen for spasticity, cholinergics for urinary retention, anticholinergics for urinary incontinence, carbamazepine or amitriptyline for painful paresthesias, and antidepressants for clinical depression.

GUILLAIN-BARRÉ SYNDROME

MNEMONIC

The 4 "A's" of Guillain-Barré syndrome—

Acute inflamm tory demyelinating polyradiculopathy
Ascending paralysis
Autonomic neuropathy
Albuminocytologic dissociation (increased albumin in CSF)

An **acute, rapidly progressive** demyelinating autoimmune disorder of the peripheral nerves that results in weakness. Also known as acute inflammatory demyelinating polyneuropathy. Associated with recent Campylobacter jejuni infection, viral infection, or influenza vaccination. Approximately 85% of patients make a complete or near-complete recovery (may take up to 1 year). The mortality rate is < 5%.

History/Pe

- Classically presents with progressive (over days), symmetric, **ascending paralysis** (distal to proximal), and **areflexia.** In severe cases, paralysis can progress to involve the trunk, diaphragm, and cranial nerves.
- Autonomic and sensory nerves may also be affected, leading to **paresthesias** and **autonomic dysregulation.**

Diagnosis

- Evidence of diffuse demyelination is seen on **nerve conduction studies,** which show ↓ nerve conduction velocity.
- Supported by a **CSF protein level > 55 mg/dL** with little or no pleocytosis (albuminocytologic dissociation).

Treatment

- Frequently monitor maximal (negative) inspiratory force (NIF) and vital capacity to determine whether patient should be admitted to ICU for impending **respiratory failure.**
- **Plasmapheresis** and **IVIG** are first-line treatments. Corticosteroids are **not indicated.**
- Aggressive physical rehabilitation is imperative.

AMYOTROPHIC LATERAL SCLEROSIS

KEY FACT

If a 55-year-old man presents with slowly progressive weakness in his left upper extremity and later in his right (upper motor neuron signs), associated with fasciculations and atrophy (lower motor neuron signs), but without bladder disturbance and with a normal cervical MRI, think ALS.

A **chronic, progressive degenerative disease,** usually of unknown etiology, that is characterized by loss of **upper and lower motor neurons.** Also known as **Lou Gehrig disease** in the United States and **motor neuron disease** in the United Kingdom. ALS has an unrelenting course and almost always progresses to respiratory failure and death, usually within 5 years of diagnosis. Men are more commonly affected than women, and onset is generally between ages 40 and 80.

History/Pe

- Presents with **asymmetric,** slowly progressive weakness (over months to years) affecting the arms, legs, diaphragm, and lower cranial nerves. Some patients initially present with **fasciculations** (muscle twitching). Weight loss is common.
- Associated with **UMN** and/or **LMN signs** (see Table 2.10-9).
- **Sensation, eye movements,** and **sphincter tone** are generally **spared.**
- Emotional lability is a common feature.

TABLE 2.10-9. UMN vs LMN Signs

Clinical Features	UMN	LMN
Pattern of weakness	Pyramidal (arm extensor and leg flexor weaknesses)	Variable
Tone	Spastic (↑)	Flaccid (↓)
DTRs	↑ (hyperreflexia)	↓ (hyporeflexia)
Miscellaneous signs	Babinski reflex, pronator drift	Atrophy, fasciculations

Diagnosis

- The clinical presentation is usually diagnostic. "Bulbar involvement" (involvement of the tongue [CN XII] or oropharyngeal muscles [CN IX, X]), suggests pathology **above the foramen magnum** and generally excludes the most common differential diagnosis, cervical spondylosis with compressive myelopathy, as a cause.
- **EMG/nerve conduction studies** reveal widespread denervation and spontaneous action potentials (fibrillation potentials). Such studies are principally performed to exclude other demyelinating motor neuropathies.
- CT/MRI of the cervical spine is done to exclude structural lesions, such as cervical spondylosis with compressive myelopathy. Especially useful in those **without bulbar involvement.**

Treatment

Supportive measures and patient education. Riluzole may delay disease progression by ↓ glutamate.

KEY FACT

Some 25% of people have "bulbar onset" ALS, which presents with difficulty swallowing, loss of tongue motility, and difficulty speaking (slurred or nasal quality).

KEY FACT

Bulbar involvement suggests pathology **above the foramen magnum,** which distinguishes ALS from cervical spondylosis with compressive myelopathy as the cause of symptoms.

Dementia

A chronic, progressive, global decline in multiple cognitive areas. **Alzheimer disease accounts for 60–80% of cases.** The differential diagnosis is described in the mnemonic **DEMENTIAS.** Take care not to confuse delirium and dementia (see the Psychiatry chapter). Table 2.10-10 and the sections below contrast the time course, diagnostic criteria, and treatment of common types of dementia.

ALZHEIMER DISEASE

Risk factors include **age,** female gender, a **family history, Down syndrome,** and low educational status. Pathology involves **neurofibrillary tangles, neuritic plaques** with **amyloid** deposition, amyloid angiopathy, and neuronal loss.

History/Pe

- Usually presents first with **amnesia** for newly acquired information (distant memory is usually intact), followed by visuospatial deficits (difficulty performing ADLs, getting lost in familiar places), language deficits, and cognitive decline that can be accompanied by depression and agitation.
- Mild cognitive impairment may precede AD by 10 years.

MNEMONIC

Differential diagnosis —

DEMENTIAS

Degenerative diseases
Endocrine
Metabolic
Exogenous
Neoplasm
Trauma
Infection
Affective disorders
Stroke/**S**tructural

TABLE 2.10-10. Types of Dementia

Type	Time Course	Pathology	Imaging/Studies
Alzheimer disease (AD)	Gradual	Diffuse atrophy with enlarged ventricles, senile plaques, and neurofibrillary tangles.	Definitive diagnosis **cannot** be made with neuroimaging at this time. MRI/CT may show diffuse cortical atrophy, especially in the temporal and parietal lobes.
Vascular dementia	Stepwise	—	Brain imaging reveals evidence of old infarctions or extensive deep white-matter changes 2° to chronic ischemia.
Frontotemporal dementia (Pick disease)	Gradual	**Pick bodies** (round intraneuronal inclusions).	MRI/CT show frontotemporal atrophy.
Normal pressure hydrocephalus (NPH)	Gradual/abrupt	—	CT/MRI reveal ventricular enlargement.
Creutzfeldt-Jakob disease (CJD)	Abrupt	Prion proteins on biopsy.	MRI with diffusion weighted imaging may show ↑ T2 and FLAIR intensity in the putamen and the head of the caudate and is also used to exclude structural brain lesions. EEG shows **periodic sharp wave complexes.**
Lewy Body dementia	Gradual	Lewy bodies (clumps of α-synuclein proteins).	MRI/CT to rule out other diagnoses.

- **Early stages:** Physical examination is generally normal except for mental status.
- **Late findings:** May include noncognitive neurologic deficits, dyspraxia (difficulty with learned motor tasks), and urinary incontinence.

Diagnosis

- **A diagnosis of exclusion** suggested by clinical features and by an insidiously progressive **cognitive decline without substantial motor impairment.**
- **Definitively diagnosed on autopsy.**
- MRI or CT may show atrophy, especially in temporal/parietal lobes, and can rule out other causes, particularly vascular dementia, NPH, and chronic subdural hematoma.
- CSF is normal.
- Neuropsychological testing can help distinguish dementia from depression.
- Hypothyroidism, vitamin B_{12} deficiency, and neurosyphilis should be ruled out.

Treatment

- **Prevention of disease progression: Cholinesterase inhibitors** (ie, donepezil) are first-line therapy for treatment of symptoms in **mild to moderate disease** but **do not affect outcome.** Memantine, an NMDA receptor antagonist, may slow decline in **moderate to severe disease.**

- **Treatment of associated symptoms:**
  - Provide supportive therapy for the patient and family.
  - Treat depression, agitation, sleep disorders, hallucinations, and delusions.

VASCULAR DEMENTIA

Dementia associated with a history of stroke and cerebrovascular disease (vascular dementia) is the second most common type of dementia.

History/Pe

- Stepwise decline in cognitive functioning.
- May be associated with other symptoms of stroke, such as **sensory** or **motor deficits.**
- Risk factors include age, hypertension, diabetes, embolic sources, and a history of stroke.

Diagnosis

Criteria for the diagnosis of vascular dementia include the presence of dementia and two or more of the following:

- Focal neurologic signs on examination.
- Symptom onset that was **abrupt,** stepwise, or related to stroke.
- Imaging is not indicated unless another etiology is suspected.

Treatment

Protocols for the prevention and treatment of vascular dementia are the same as those for stroke.

KEY FACT

If a patient shows abrupt changes in symptoms over time rather than a steady decline, think vascular dementia.

FRONTOTEMPORAL DEMENTIA (PICK DISEASE)

A **rare,** progressive form of dementia characterized by **atrophy of the frontal and temporal lobes.**

History/Pe

- Patients present with **disinhibition** and **significant changes in behavior and personality early in the disease.** Other symptoms include speech disturbance, inattentiveness, compulsive behaviors, and occasionally extrapyramidal signs.
- Frontotemporal dementia rarely begins after age 75.

Diagnosis

The diagnosis is suggested by clinical features and by evidence of frontotemporal atrophy seen on MRI or CT.

Treatment

Treatment is symptomatic.

Q

A 71-year-old woman is brought to her primary care physician's office by her son, who is concerned that she has had worsening memory, difficulty participating in her daily activities, restlessness, and difficulty sleeping for the past year. She scores a 22 on the Mini-Mental State Examination (MMSE). What is the most likely diagnosis?

NORMAL PRESSURE HYDROCEPHALUS

A **potentially treatable** form of dementia that is thought to arise from impaired reabsorption of CSF.

KEY FACT

NPH = "**W**et (incontinence), **W**obbly (gait apraxia), and **W**acky (dementia)."

History/Pe

Symptoms include the **classic triad of dementia, gait apraxia, and urinary incontinence.** Headaches and other signs of ↑ ICP (eg, papilledema) typically do not appear, although continuous ICP monitoring may reveal spikes of elevated pressure.

Diagnosis

- Suggested by clinical features; gait is classically described as "magnetic" or with "feet glued to the floor."
- CT or MRI shows ventricular enlargement out of proportion to sulcal atrophy (see Figure 2.10-6).
- LP reveals normal CSF pressures and can be therapeutic.

Treatment

LP or continuous lumbar CSF drainage for several days may cause clinically significant improvement of the patient's symptoms. If so, surgical ventriculoperitoneal shunting is the treatment of choice.

CREUTZFELDT-JAKOB DISEASE

Although it is the most common **prion disease,** CJD remains an extremely rare form of dementia. CJD is a member of the transmissible **spongiform encephalopathies,** all of which are characterized by spongy degeneration, neuronal loss, and astrocytic proliferation. In CJD, an abnormal protease-resistant prion protein accumulates in the brain.

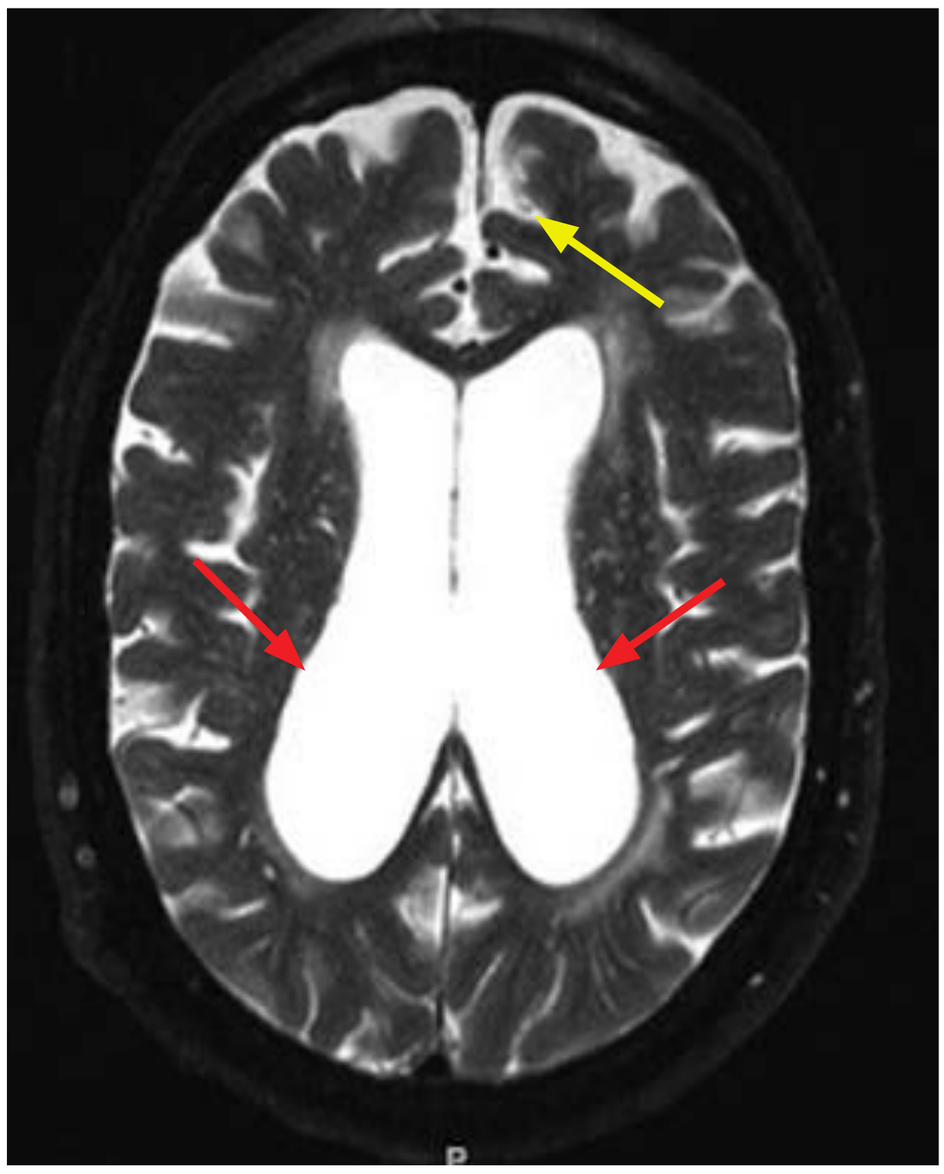


FIGURE 2.10-6. Normal pressure hydrocephalus. T2-weighted MRI from a 60-year-old woman with slowly developing urinary incontinence, gait instability, and early dementia shows marked dilation of the lateral ventricles (red arrows). This is out of proportion to the sulci (yellow arrow), which appear normal. (Reproduced with permission from USMLE-Rx.com.)

A

Alzheimer disease is the likely diagnosis. The key differences between AD and normal aging is that in normal aging, patients can perform their activities of daily living, complain of memory loss yet provide detailed information about their forgetfulness, and have a score > 24 on the MMSE.

History/Pe

- CJD causes a **subacute dementia** with ataxia and/or startle-induced **myoclonic jerks** with **rapid** clinical progression that is noted weeks to months after symptom onset.
- New-variant CJD (mad cow disease) is a more slowly progressive prion disease seen in younger people with a history of eating contaminated beef or contaminated human brains (kuru).

KEY FACT

CJD's rapid progression and presence of myoclonus distinguish it from other dementias.

Diagnosis

- Suggested by clinical features.
- The differential diagnosis includes limbic encephalitis, Hashimoto (steroid-responsive) encephalopathy, and toxic encephalopathy (eg, lithium or bismuth).
- Elevated levels of CSF 14-3-3 and tau protein are seen, indicating rapid destruction of neurons.
- Definitive diagnosis can be made only by brain biopsy or autopsy, but MRI or EEG (for detection of periodic sharp wave complexes) may be helpful. Specimens must be handled with special precautions to prevent transmission.

Treatment

Currently, there is no effective treatment. Most patients die within 1 year of symptom onset.

LEWY BODY DEMENTIA

Dementia of unclear etiology characterized by progressive cognitive changes, visual hallucinations, and Parkinson-like movement abnormalities such as bradykinesia.

History/Pe

- **Physical and cognitive symptoms** may present around the same time and include:
  - **Physical:** Bradykinesia, rigidity, tremor and shuffling gait with narrow-leg stance
  - **Cognitive:** Progressive problems with visual-spatial processing, attention, executive dysfunction and memory.
- **Psychiatric symptoms** are common and can include hallucinations, delusions, depression, and anxiety.

Diagnosis

- Usually clinical.
- Imaging and/or neuropsychological evaluation to rule out other diagnoses.
- Definitive diagnosis via brain biopsy or autopsy. Specimens will reveal abnormal clumps of α-synuclein proteins within neurons (Lewy bodies).

Treatment

Symptomatic treatment; no disease-modifying agents are available.

Q

A 65-year-old man presents to his internist with 10 years of bilateral hand tremors. His mother and older brother have similar tremors. He denies difficulty concentrating, trouble with rising from seated positions, or recent falls. What is the most likely diagnosis?

Movement Disorders

HUNTINGTON DISEASE

KEY FACT

If a 43-year-old man presents with gradual onset of chorea, irritability, and behavioral disturbances and his father experienced these symptoms at a slightly older age, think Huntington disease.

A rare, **hyperkinetic, autosomal dominant** disease involving multiple **abnormal CAG triplet repeats** within the HD gene on chromosome 4. The number of repeats typically expands in subsequent generations, leading to earlier expression and more severe disease **(anticipation).** Life expectancy is 20 years from the time of diagnosis.

History/Pe

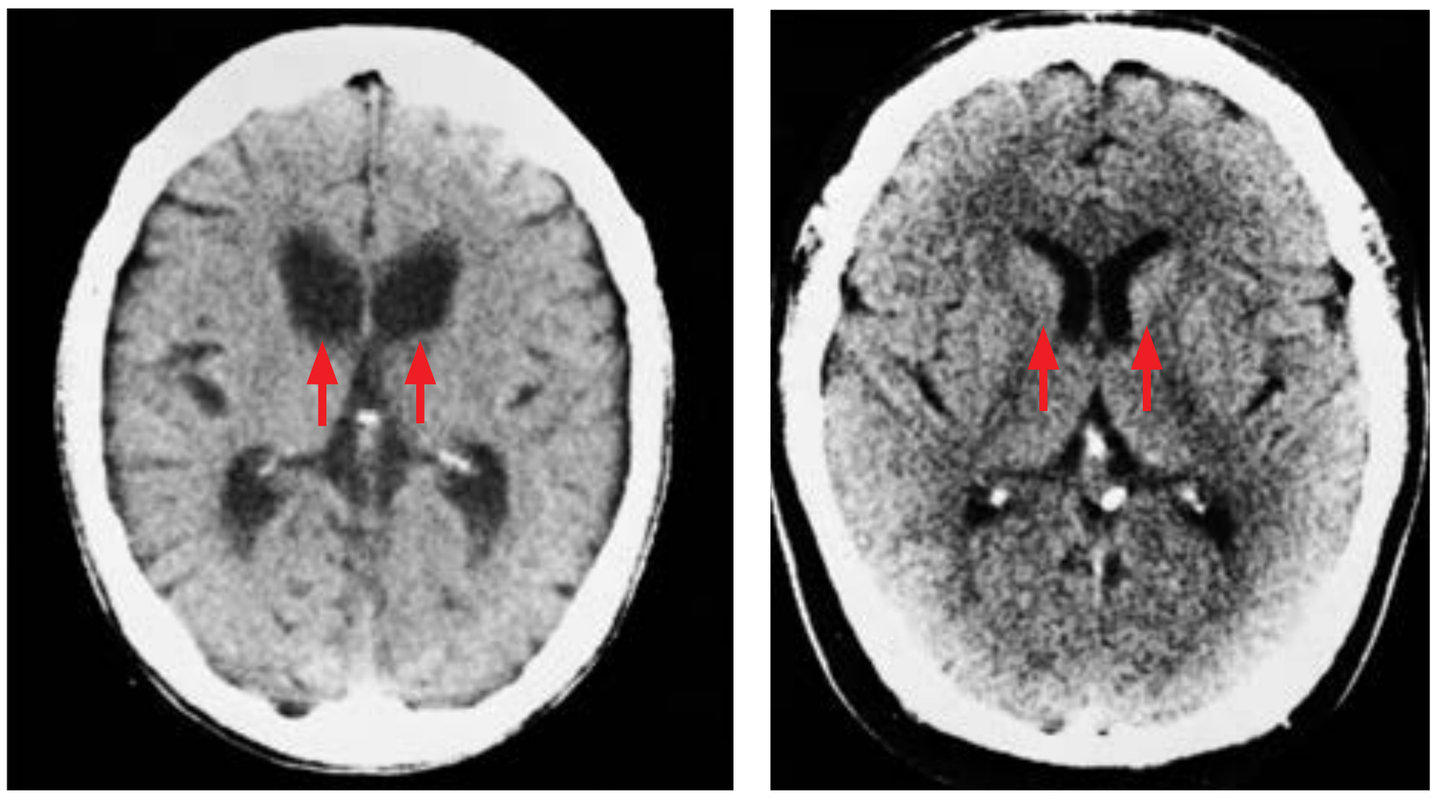
- Presents at 30–50 years of age with gradual onset of **chorea** (purposeless, involuntary dancelike movements), **altered behavior,** and **dementia** (begins as irritability, clumsiness, fidgetiness, moodiness, and antisocial behavior).
- Weight loss and depression may also be seen.

Diagnosis

- Clinical diagnosis confirmed by genetic testing.
- CT/MRI show cerebral atrophy (especially of the **caudate** and **putamen;** see Figure 2.10-7).

Treatment

- There is no cure, and disease progression cannot be halted. Treat symptomatically.
- Reserpine or tetrabenazine can be given to minimize unwanted movements. Psychosis should preferably be treated with atypical antipsychotics to ↓ the risk of extrapyramidal side effects or tardive dyskinesia. SSRIs are first-line therapy for depression.
- Genetic counseling should be offered to offspring.



A B

FIGURE 2.10-7. Atrophy of the cerebral and caudate nuclei in Huntington disease. (A) Noncontrast CT in a 54-year-old patient with Huntington disease shows atrophy of the caudate nuclei (arrows) and diffuse cerebral atrophy with dilation of the lateral ventricles. **(B)** A normal 54-year-old subject (arrows on caudate nuclei). (Reproduced with permission from Ropper AH, Samuels MA. Adams & Victor's Principles of Neurology, 9th ed. New York, NY: McGraw-Hill; 2009.)

A

Essential tremor is the most likely diagnosis. Unlike the resting tremor in Parkinson disease, essential tremors are suppressed at rest and exacerbated with movements. Remember that bilateral tremors are less common in early Parkinson disease, and patients with Parkinson disease are more likely to present with multiple symptoms. Treat essential tremors with propranolol, primidone, and topiramate.

PARKINSON DISEASE

An **idiopathic** disorder that usually begins after age 50 and is caused by **dopamine depletion** in the **substantia nigra.** Parkinsonism (nonidiopathic) has symptoms similar to Parkinson disease and can be caused by **antipsychotic use,** multiple subcortical infarcts ("vascular parkinsonism"), toxin ingestion, and trauma.

History/Pe

- The **"Parkinson tetrad"** consists of the following:
  - **Resting tremor** (eg, "pill rolling") with a frequency of **4–6 Hz** that **decreases with voluntary movement.**
  - **Rigidity:** "Cogwheeling."
  - **Bradykinesia:** Slowed movements as well as difficulty initiating movements. Festinating gait (small, shuffling steps) without arm swing is also seen.
  - **Postural instability:** Stooped posture, impaired righting reflexes, falls.
- **Other manifestations:** Masked facies, memory loss, and micrographia.

Treatment

- Amantadine has mild antiparkinsonian activity and may improve akinesia, rigidity, and tremor. It can be used for temporary, short-term monotherapy early in the course of the disease.
  - **Side effects:** Ankle edema and livedo reticularis.
- **Levodopa/carbidopa** combination therapy is the mainstay of treatment. Levodopa is a dopamine precursor that can cross the blood-brain barrier. Carbidopa blocks the peripheral conversion of levodopa to prevent the side effects of levodopa (nausea and vomiting).
  - **Early side effects: Hallucinations,** dizziness, headache, and agitation.
  - **Late side effects:** Involuntary movements.
- **Dopamine agonists** (ropinirole, pramipexole, bromocriptine) can be used for treatment in early disease.
  - **Side effects:** Hypotension, somnolence, **confusion, hallucinations,** and **compulsive gambling.**
- **Selegiline** (an MAO-B inhibitor) may be neuroprotective and may ↓ the need for levodopa.
  - **Side effects: Confusion** and insomnia.
- **Catechol-O-methyltransferase (COMT) inhibitors** (entacapone or tolcapone) are not given alone but ↑ the availability of levodopa to the brain and may ↓ motor fluctuations.
- **Anticholinergics** (trihexyphenidyl or benztropine)—generally used in younger patients whose primary symptom is tremor.
  - **Side effects:** Dry mouth, blurred vision, constipation, nausea, and urinary retention.
- If medical therapy is insufficient, **surgical pallidotomy** or **deep brain stimulators** may produce clinical benefit.

KEY FACT

A significant difference between the gait abnormalities of Parkinson disease and that of NPH is **preservation of arm swing in NPH.**

MNEMONIC

Parkinson disease causes people to feel **TRAP**ped—

Tremor ("pill rolling")
Rigidity (cogwheeling)
Akinesia/bradykinesia
Postural instability

KEY FACT

- Parkinson disease—dopamine deficiency, ACh excess.
- Alzheimer disease—ACh and norepinephrine deficiencies.
- Myasthenia gravis—blocked ACh activity.

Neoplasms

Intracranial neoplasms may be 1° (30%) or **metastatic (70%).**

- Of all 1° brain tumors, 40% are benign, and these rarely spread beyond the CNS.
- Metastatic tumors are most often from 1° **lung, breast, kidney, and GI tract neoplasms** and **melanoma.** They occur at the gray-white junction;

KEY FACT

Most CNS tumors are metastatic. The most common 1° CNS tumors in adults are glioblastoma multiforme and meningiomas. The most common 1° CNS tumors in children are astrocytomas followed by medulloblastomas.

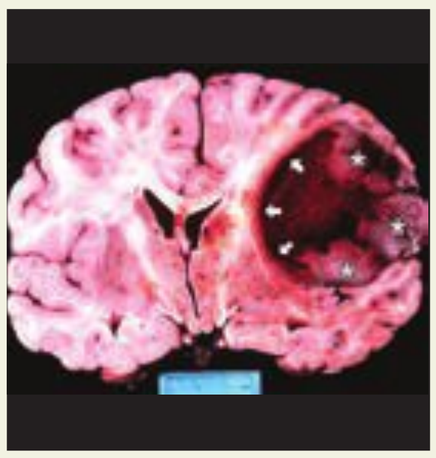
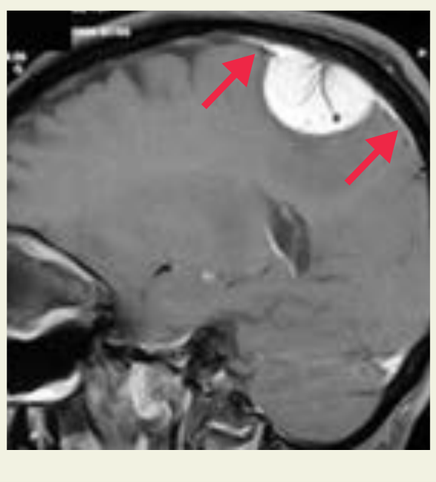
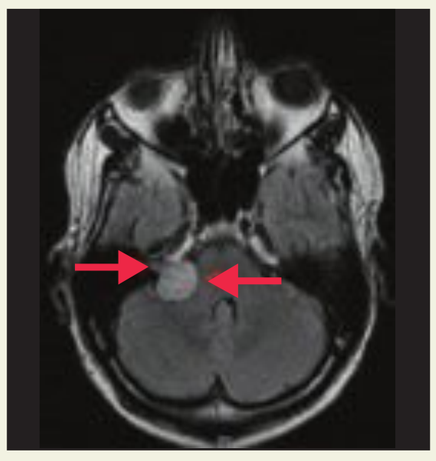
may be multiple discrete nodules; and are characterized by **rapid growth, invasiveness, necrosis,** and **neovascularization.**

- More common in **men** than in women, except for meningiomas.

History/Pe

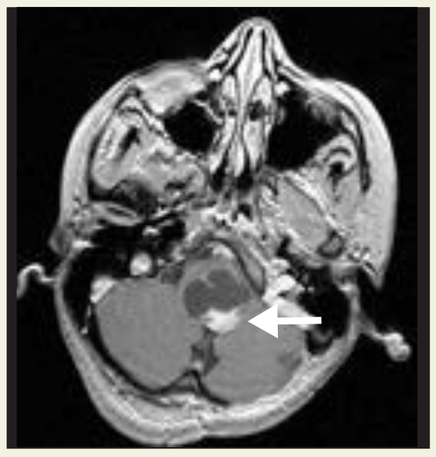
- Symptoms depend on tumor type and location (see Tables 2.10-11 and 2.10-12), local growth and **resulting mass effect,** cerebral edema, or ↑ ICP 2° to ventricular obstruction. Although headaches are often thought of as the main presenting symptom, **only 31% of patients present with headache** at diagnosis, and only 8% have headache as the sole presenting feature.

TABLE 2.10-11. Common 1° Neoplasms in Adults

tuMor	benign vS Malignant	preSentation	treatMent
Astrocytoma (diffus , anaplastic, grade IV/ **glioblastoma**) 	Diffus —benign Anaplastic—malignant Glioblastoma—malignant	Presentation of astrocytomas depends on location of tumor. Some symptoms include headache, seizures, or focal deficit . Glioblastoma is the most common malignant 1° brain tumor. Progresses rapidly and has a poor prognosis (< 1 year from the time of diagnosis).	Surgical removal/resection. Radiation and chemotherapy have variable results.
Meningioma 	Generally benign	Presentation depends on location; often related to cranial neuropathy or is an incidental findin .	Surgical resection; radiation for unresectable tumors.
Vestibular schwannoma (aka acoustic neuroma) 	Generally benign	Unilateral hearing loss, tinnitus, vertigo, and loss of balance. Bilateral in NF2.	Surgical resection, radiation, or monitoring.

Glioblastoma multiforme and meningioma images reproduced with permission from the US Department of Health and Human Services and Armed Forces Institute of Pathology. Schwannoma figu e reproduced with permission of Lars.linus/Wikimedia Commons.

TABLE 2.10-12. Common 1° Neoplasms in Children

tuMor	pathology	preSentation	treatMent
Pilocytic astrocytoma 	Generally benign, well circumscribed, stain ⊕ for GFAP. **Posterior fossa/infratentorial tumor.**	Presents with drowsiness, headache, ataxia, nausea, vomiting, cranial neuropathy. Slow-growing with **protracted course.**	Resection if possible; radiation.
Medulloblastoma 	A primitive **neuroectodermal** tumor. Arises from the fourth ventricle or cerebellar vermis and causes ↑ ICP. **Posterior fossa/ infratentorial tumor.**	**Highly malignant but radiosensitive;** may seed the subarachnoid space. May cause obstructive hydrocephalus.	Surgical resection coupled with radiation and chemotherapy.
Craniopharyngioma 	The most common **suprasellar** tumor in children. **Calcifi ation** is common.	Benign. May cause hypopituitarism or homonymous hemianopsia.	Surgical resection.

MRI of pilocytic astrocytoma reproduced with permission from Hafez RFA. Stereotaxic gamma knife surgery in treatment of critically located pilocytic astrocytoma: preliminary result, World J Surg Oncol 2007 Mar 29;5:39. CT of medulloblastoma reproduced with permission from US Department of Health and Human Services and Armed Forces Institute of Pathology. CT of craniopharyngioma reproduced with permission from Garnet MR, Puget S, Grill J, et al. Craniopharyngioma, Orphanet J Rare Dis. 2007 Apr 10;2:18.

- Seizures or slowly progressive focal motor deficits are the most common presenting features.
- When ↑ ICP is the presenting feature, symptoms include **headache, nausea/vomiting,** and diplopia (false localizing CN VI palsies). In the era of neuroimaging, it is relatively **rare** for patients to present with ↑ ICP.
- **Other presenting symptoms:** Visual field abnormalities, neurologic deficits, psychiatric symptoms.

Diagnosis

- CT and MRI with and without contrast to localize and determine the extent of the lesion.
  - Gadolinium-enhanced MRI is generally better for visualizing soft tissue tumors and vascularity.

KEY FACT

Most common cancers that metastasize to brain:
Lung and Skin **G**o to the **BR**ain: Lung, Skin, **GI**, **B**reast, **R**enal.

- CT is preferred for evaluating skull base lesions and for emergencies (eg, obstructive hydrocephalus) when an MRI cannot be rapidly acquired.
- Histologic diagnosis via CT-guided biopsy or surgical biopsy.

Treatment

- **Resection** (if possible), **radiation,** and **chemotherapy.**
- Therapy is highly dependent on tumor type, histology, progression, and site (see Tables 2.10-11 and 2.10-12).
- If ICP is ↑, manage ICP with:
  - Head elevation (↑ venous outflow from brain).
  - Hyperventilation (↓ CO_2 leads to cerebral vasoconstriction resulting in ↓ vasogenic edema).
  - Corticosteroids (↓ vasogenic edema).
  - Mannitol (extraction of free water from brain via osmotic diuresis).
  - Removal of CSF.
- AEDs can be used in patients who have had a seizure.

KEY FACT

Two-thirds of 1° brain tumors in **adults** are **supratentorial. One-third** of those in **children** are **supratentorial.**

KEY FACT

Symptoms of ↑ ICP:
- Nausea
- Vomiting
- Diplopia
- Headache that is worse in the morning, with bending over, or with recumbency

Neurocutaneous Disorders

NEUROFIBROMATOSIS

The most common neurocutaneous disorder. There are **two major types:** neurofibromatosis 1 (NF1, or von Recklinghausen syndrome) and neurofibromatosis 2 (NF2). Both are **autosomal dominant** diseases.

History/Pe

- Diagnostic criteria for **NF1** include **two or more** of the following:
  - Six **café-au-lait spots** (flat, uniformly hyperpigmented macules).
  - Two neurofibromas (benign peripheral nerve sheath tumors) of any type (see Figure 2.10-8).
  - **Freckling in the axillary or inguinal area.**
  - **Optic glioma.**
  - Two **Lisch nodules** (pigmented iris hamartomas).
  - Bone abnormality (eg, kyphoscoliosis).
  - A **first-degree relative** with NF1.
- Diagnostic criteria for **NF2** are as follows:
  - **Bilateral vestibular schwannomas** (also known as **acoustic neuromas**).
  - First-degree relative with NF2 and **either:**
    - Unilateral acoustic neuromas or
    - Two of any of the following tumor types: neurofibromas, meningiomas, gliomas, or schwannoma.
  - Other features include seizures, skin nodules, and café au lait spots.



FIGURE 2.10-8. Neurofibromas associated with neurofibromatosis
(Reproduced with permission from USMLE-Rx.com.)

KEY FACT

NF1 and NF2 are clinically evident by ages 15 and 20, respectively.

KEY FACT

Vestibular schwannomas (also known as **acoustic neuromas**) present with ipsilateral tinnitus, hearing loss, vertigo. Tx of choice = surgical resection.

Diagnosis

- **MRI** of the brain, brainstem, and spine with gadolinium.
- Conduct a complete dermatologic exam, ophthalmologic exam, and family history. Auditory testing is recommended.

Treatment

- There is **no cure;** treatment is symptomatic (eg, **surgery** for kyphoscoliosis or **debulking of tumors**).
- **Vestibular schwannomas** (see Table 2.10-11) and optic gliomas can be treated with surgery or radiosurgery. Meningiomas can be resected.

TUBEROUS SCLEROSIS

Autosomal dominant disorder that affects **many organ systems,** including the CNS, skin, heart, retina, and kidneys.

History/Pe

- Presents with **infantile spasms** or **seizures, "ash-leaf" hypopigmented lesions** (Figure 2.10-9A) on the trunk and extremities, and **mental disability** (↑ likelihood with early age of onset).
- Other skin manifestations include **sebaceous adenomas** (small red nodules on the nose and cheeks in the distribution of a butterfly; Figure 2.10-9B) and a **shagreen patch** (a rough papule in the lumbosacral region with an orange-peel consistency).
- Other symptoms are 2° to small benign tumors that grow on the face, eyes, brain, kidney, and other organs. For example:
  - CHF from cardiac rhabdomyoma; renal disease from renal cysts, angiolipomas, or carcinomas.
  - Developmental disability from brain lesions.

Diagnosis

- Usually clinical.
- **Ash-leaf** lesions are enhanced by a **Wood UV lamp.**
- **Imaging:**
  - **MRI of brain:** Evaluate for subependymal giant cell astrocytoma and calcified tubers (potato-like nodules) within the cerebrum in the periventricular area. If lesions obstruct CSF outflow, obstructive hydrocephalus can develop.
  - **Echocardiography:** Evaluate for rhabdomyoma of the heart, especially in the apex of the left ventricle (affects > 50% of patients).
  - **MRI of abdomen:** Evaluate for renal disease (cysts, angiolipoma, and/or carcinoma).
  - **EEG:** Evaluate for seizure activity.



A B

FIGURE 2.10-9. Tuberous sclerosis. (A) "Ash-leaf" macules on a patient with tuberous sclerosis and **(B)** sebaceous adenomas in a butterfly distribution. (Part A reproduced with permission from Tonekaboni SH, Tousi P, Ebrahimi A, et al. Clinical and para clinical manifestations of tuberous sclerosis: a cross sectional study on 81 pediatric patients, Iran J Child Neurol 2012 Summer;6(3):25-31. Part B adapted with permission from Fred H, van Dijk H. Images of memorable cases: case 143. Connexions Web site. December 4, 2008. Available at: http://cnx.org/content/m14923/1.3/.)

KEY FACT

Infantile spasms occur in children < 3 and can consist of head bobbing, fexor spasms, extensor spasms, or movements that mimic the startle response. They may be associated with psychomotor regression or behavioral changes.

Q 1

A 61-year-old man presents to the ED with a 6-month history of progressively worsening nausea and morning headache. Patient is in no apparent acute distress. What is the preferred diagnostic study?

Q 2

A 82-year-old woman presents to the ED with a 2-day history of difficulty speaking and weakness in her right face and arm. During the interview, she speaks in two- to three-word choppy sentences but can follow commands. She cannot repeat what you say. Where is her lesion?

Q 3

A 45-year-old white man presents to the ED with sudden-onset headache and a dilated pupil in his right eye that is nonreactive to light. His right eye is hard to the touch. What is the most likely diagnosis, and what medications should be avoided in this patient?

KEY FACT

So many names, it's a wonder we are talking about aphasias!

- Broca aphasia = motor aphasia, expressive aphasia, or nonfluent aphasia.
- Wernicke aphasia = sensory aphasia, receptive aphasia, or fluent aphasia.

KEY FACT

In true Broca and Wernicke aphasia, repetition is impaired. If repetition is intact, the deficit is called transcortical motor aphasia (TMA) or transcortical sensory aphasia (TSA), which is due to a lesion around the Broca and Wernicke areas, respectively.

1 **A**

This patient presents with symptoms that are concerning for increased ICP. As he is not in acute distress, MRI is the preferred study because it is better for visualizing soft tissue and vascularity.

2 **A**

This patient presents with Broca aphasia. In Broca aphasia, the lesion is in the posterior frontal cortex of the dominant side of the brain, in this case the left.

3 **A**

This patient presentation is consistent with closed-angle glaucoma. Avoid pupil-dilating medications such as atropine, which will ↑ IOP and prevent drainage of aqueous humor.

Treatment

- Treatment should be based on symptoms (eg, cosmetic surgery for facial sebaceous adenomas).
- Treat seizures if present. If infantile spasms are present, treat with ACTH or vigabatrin.
- Surgical intervention may be indicated in the setting of ↑ ICP from obstructive hydrocephalus or for seizures associated with an epileptogenic focus or severe developmental delay.

Aphasia

A general term for speech and language disorders. Usually results from lesions (eg, strokes, tumors, abscesses) in the "dominant hemisphere." The left hemisphere is dominant in > 95% of right-handed people and 60–80% of left-handed people.

BROCA APHASIA

A **disorder of spoken and/or written language production, with intact comprehension.** Due to an insult to Broca area in the **posterior inferior frontal cortex** (see Figure 2.10-10). Often 2° to a left superior **MCA stroke.** Also known as **motor aphasia.**

History/Pe

Presents with **impaired speech production, frustration** with awareness of deficits, arm and facial **hemiparesis,** hemisensory loss, and apraxia of the oral muscles. Speech is described as "telegraphic" with few words and frequent pauses.

Treatment

Speech therapy (varying outcomes with intermediate prognosis).

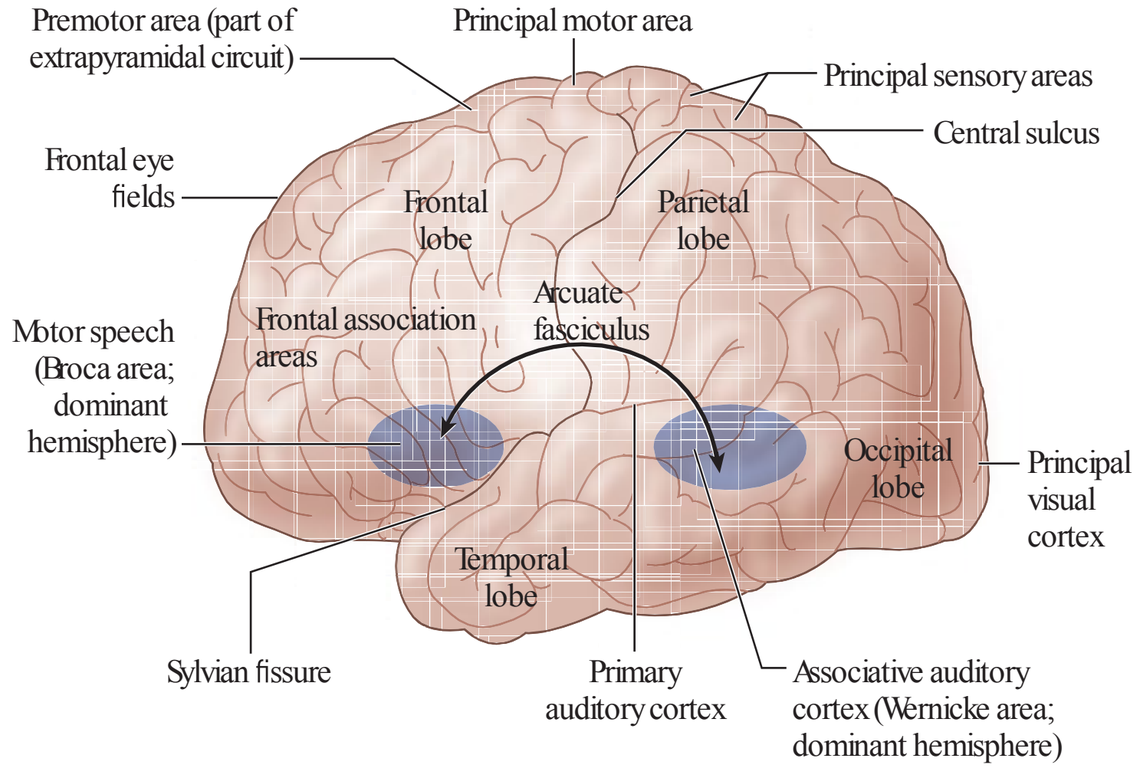


FIGURE 2.10-10. Cerebral cortex with Broca and Wernicke areas highlighted. (Reproduced with permission from Waxman SG. Clinical Neuroanatomy, 26th ed. New York, NY: McGraw-Hill; 2010.)

WERNICKE APHASIA

- A **disorder of language comprehension with intact yet nonsensical production.**
- Due to an insult to Wernicke area in the left posterior superior temporal (perisylvian) lobe. Often 2° to left **inferior/posterior MCA** embolic stroke (see Figure 2.10-10).

History/PE

Presents with **preserved fluency** of language with impaired repetition and comprehension, leading to **"word salad."** Patients are unable to follow commands; make frequent use of **neologisms** (made-up words) and paraphasic errors (word substitutions); and show **lack of awareness** of deficits.

Treatment

Treat the underlying etiology and institute speech therapy.

KEY FACT

BROca is **BRO**ken and **W**ernicke is **W**ordy.

Coma

Unconsciousness marked by limited to no response to stimuli (ie, a state of unarousable unresponsiveness). Lesser states of impaired arousal are known as "obtundation" or "stupor." Coma is caused by dysfunction of both cerebral hemispheres or the brainstem (pons or higher) due to structural or toxic-metabolic insults. Causes include the following:

- **Diffuse hypoxic/ischemic encephalopathy** (eg, postcardiac arrest).
- **Diffuse axonal injury** from high-acceleration trauma (eg, motor vehicle accidents).
- **Brain herniation** (eg, cerebral mass lesion, SAH with obstructive hydrocephalus).
- **Widespread infection** (eg, viral encephalitis or advanced bacterial meningitis).
- **Massive brainstem hemorrhage or infarction.**
- Central pontine myelinolysis.
- **Electrolyte disturbances** (eg, hypoglycemia).
- **Exogenous toxins** (eg, opiates, benzodiazepines, EtOH, other drugs).
- Generalized **seizure** activity or postictal states.
- **Endocrine** (eg, severe hypothyroidism) or **metabolic dysfunction** (eg, thiamine deficiency).

History/PE

- Obtain a complete medical history from witnesses, including current medications (eg, **sedatives**).
- Conduct thorough medical and neurologic exams, including assessments of mental status, spontaneous motor activity, muscular tone, breathing pattern, funduscopy, pupillary response, eye movements, corneal reflex, gag reflex, and motor or autonomic responses to noxious stimuli applied to the limbs, trunk, and face (eg, retromandibular pressure, nasal tickle).

Diagnosis

- Typically made by a combination of the history/physical and laboratory tests or neuroimaging.
- Check glucose, electrolytes, calcium, a renal panel, LFTs, ABGs, a toxi-

Q

A 39-year-old man presents to the ED with severe eye pain, photophobia, and a persistent sensation that something is in his eye. You are suspicious of a corneal abrasion. What are the risk factors for this condition, and what diagnostic test can you do to confirm your suspicion?

TABLE 2.10-13. Differential Diagnosis of Minimally Conscious State

Variable	"Locked-in" Syndrome	PVS	Coma	Brain death
Alertness	Wakeful and alert with retained cognitive abilities.	Wakefulness without awareness. Eyes open and close—sleep-wake cycles present.	Unconscious; Eyes closed—no sleep-wake cycles.	Unconscious; no sleep-wake cycles.
Most common causes	Central pontine myelinolysis, brainstem stroke, advanced ALS.	Diffuse cortical injury or hypoxic ischemic injury.	Diffuse hypoxic encephalopathy, widespread infection, electrolyte disturbances, toxins.	Same as coma.
Voluntary motor ability	Eyes and eyelids.	None.	None.	None.
Respiratory drive	Yes.	Yes.	Yes.	None.

cology screen, and blood and CSF cultures. Other metabolic tests (eg, TSH) may be performed based on the clinical index of suspicion.

- Obtain a **head CT without contrast** before other imaging to evaluate for hemorrhage or structural changes. Imaging should **precede LP** in light of the risk of herniation.
- Obtain an MRI to exclude structural changes and ischemia (eg, brainstem).
- Rule out catatonia, conversion unresponsiveness, **"locked-in" syndrome,** or **persistent vegetative state** (PVS), all of which can be confused with true coma (see Table 2.10-13).

Treatment

Initial treatment should consist of the following measures:

- **Stabilize the patient:** Attend to **ABCs.**
- **Reverse the reversible:** Administer **DONT—D**extrose, **O**xygen, **N**alox-one, and **T**hiamine.
- **Identify and treat the underlying cause** and associated complications.
- **Prevent further damage.**

KEY FACT

Artificial life support can be discontinued **only** after two physicians have declared the patient legally brain dead.

Nutritional Deficiencie

Table 2.10-14 describes neurologic syndromes commonly associated with nutritional deficiencies.

A

Risk factors of corneal abrasion include trauma, foreign body, and contact lens use. Use a penlight to document pupillary function and presence/absence of a foreign body. **Fluorescein exam** can be diagnostic and will show a corneal staining defect.

Ophthalmology

VISUAL FIELD DEFECTS

Figure 2.10-11 illustrates common visual field defects and the anatomic areas with which they are associated.

TABLE 2.10-14. Neurologic Syndromes Associated with Nutritional Deficiencie

Vitamin	Syndrome	Signs/Symptoms	Classic patients	treatment
Thiamine (vitamin B_1)	Wernicke encephalopathy	The classic triad consists of **encephalopathy, ophthalmoplegia,** and **ataxia.**	**Alcoholics, hyperemesis, starvation, renal dialysis,** AIDS. **Can be brought on or exacerbated by high-dose glucose administration.**	Reversible almost immediately with thiamine administration. Always give thiamine before glucose.
	Korsakoff dementia	Above plus **anterograde and retrograde amnesia,** horizontal nystagmus, and **confabulations.**	Same as above. Usually occurs in Wernicke syndrome that was treated too late or inadequately.	Irreversible.
Cyanocobalamin (vitamin B_{12})[a]	**Peripheral neuropathy;** Combined system disease (CSD)	Gradual, progressive onset. Symmetric paresthesias, stocking-glove sensory neuropathy, leg stiffness, spasticity, paraplegia, bowel and bladder dysfunction, sore tongue, and dementia. Associated with elevated methylmalonic acid levels.	Patients with pernicious anemia; strict vegetarians; status post gastric or ileal resection; ileal disease (eg, Crohn); alcoholics or others with malnutrition.	B_{12} injections or large oral doses.
Folate[a]	Folate deficiency	Irritability; personality changes without the neurologic symptoms of CSD.	Alcoholics.	Reversible if corrected early.

[a]Associated with ↑ homocysteine and an ↑ risk of vascular events.

GLAUCOMA

In the eye, aqueous humor produced by the ciliary body on the iris travels through the pupil into the anterior chamber, and is then drained back into the bloodstream via the trabecular meshwork in the angle of the anterior chamber.

- Any process that disrupts this natural flow can ↑ **intraocular pressure (IOP),** damaging the optic nerve and causing visual field deficits. Glaucoma is the result of such damage to the nerve.
- Open-angle glaucoma is much more common in the United States than closed-angle glaucoma (see Figure 2.10-12 and Table 2.10-15).

KEY FACT

Closed-angle glaucoma headaches are triggered by darkness (due to pupillary dilation). Migraine headaches are triggered by bright lights.

KEY FACT

Open-angle glaucoma generally occurs bilaterally, but closed-angle glaucoma occurs unilaterally.

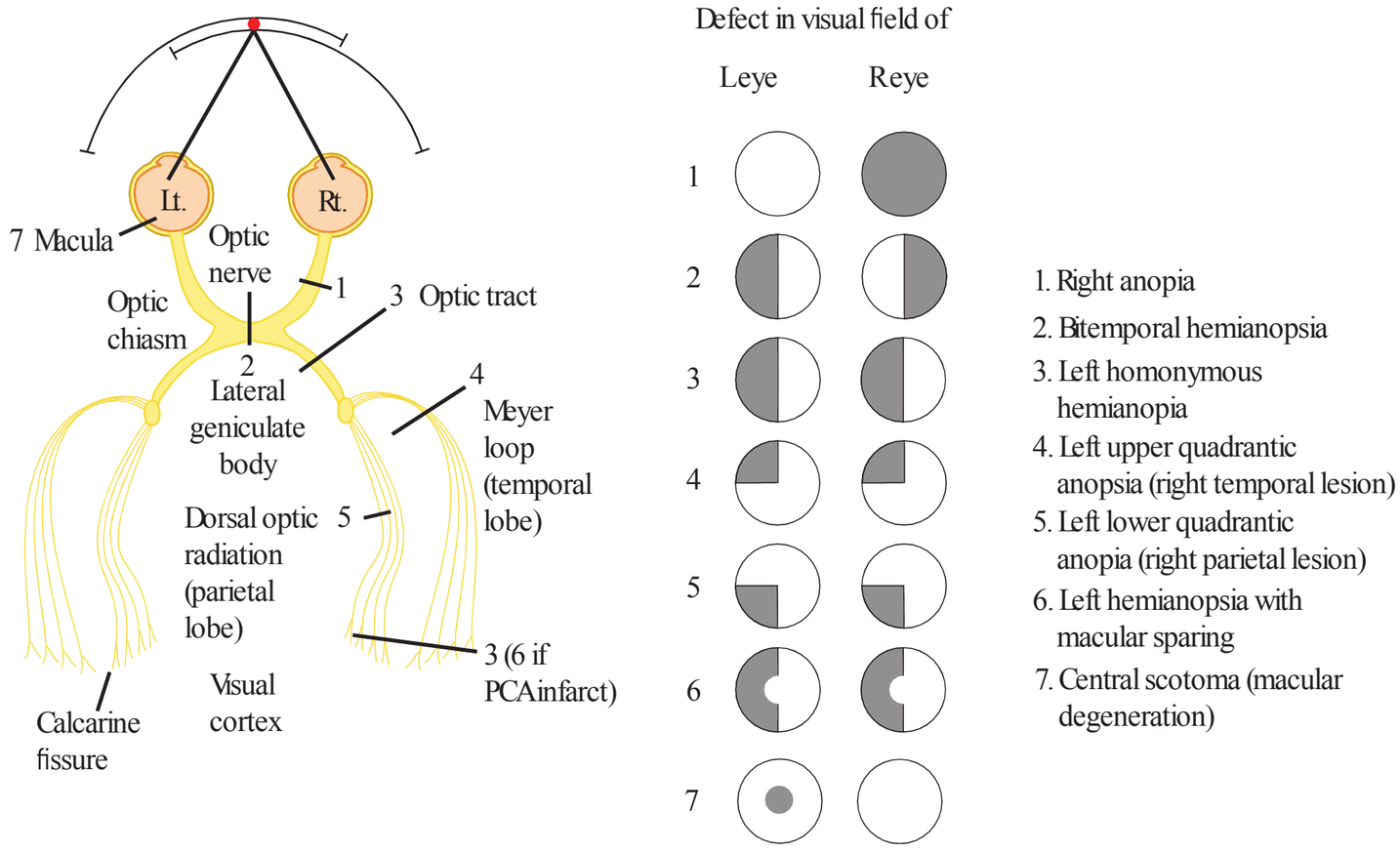


FIGURE 2.10-11. Visual field defects **(1)** Right anopsia. **(2)** Bitemporal hemianopsia (pituitary lesion, chiasm). **(3)** Left homonymous hemianopsia. **(4)** Left upper quadrantic anopsia (right temporal lesion, MCA). **(5)** Left lower quadrantic anopsia (right parietal lesion, MCA). **(6)** Left hemianopsia with macular sparing (PCA infarct). **(7)** Central scotoma (macular degeneration). (Reproduced with permission from Le T et al. First Aid for the USMLE Step 1 2015. New York, NY: McGraw-Hill; 2015.)

CATARACTS

Lens opacification resulting in obstructed passage of light. Associated with diabetes, hypertension, advanced age, and exposure to radiation.

History/Pe

Presents with loss of visual acuity and difficulty with night vision.

Treatment

Surgical lens removal and replacement.

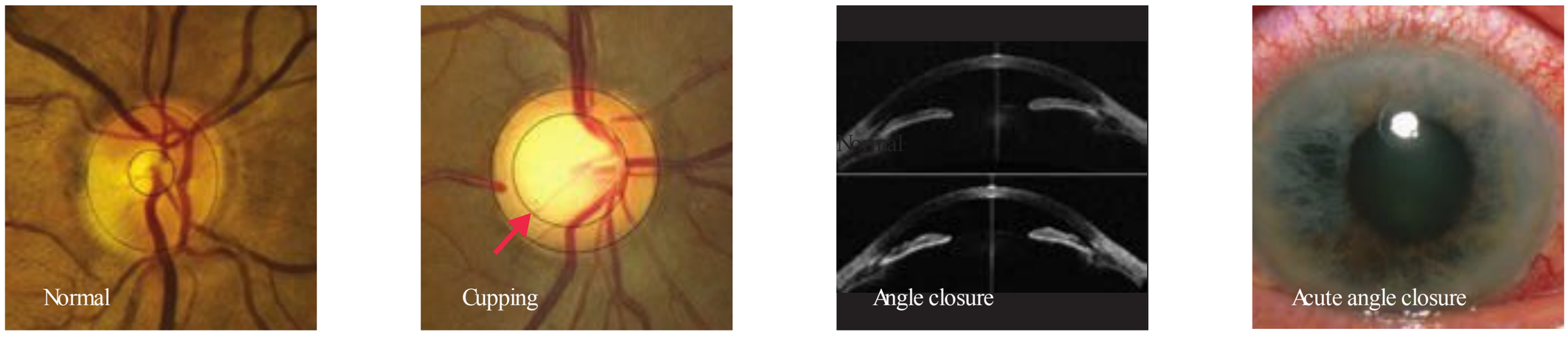


FIGURE 2.10-12. Findings in open- and closed-angle glaucoma. **(A)** Normal optic disk. **(B)** Cupping (increased cup-to-disk ratio) seen in open-angle glaucoma. **(C)** Iris, pupil, and cornea in normal eye compared to eye with closed-angle glaucoma. **(D)** Fixed, dilated pupil seen in closed-angle glaucoma. (Parts A, B reproduced with permission from EyeRounds. Part C reproduced with permission from Low S et al. Autosomal dominant Best disease with an unusual electrooculographic light rise and risk of angle-closure glaucoma: a clinical and molecular genetic study, Mol Vis 2011;17:2272–2282. Part D used with permission from Dr. Jonathan Trobe.)

TABLE 2.10-15. Closed-Angle vs Open-Angle Glaucoma

	Closed-angle glaucoma	Open-angle glaucoma
Etiology	Disrupted flow of aqueous humor into the anterior chamber results in ↑ pressure in the posterior chamber, leading to angle closure that ↓ drainage.	Diseased trabecular meshwork results in ↓ drainage leading to gradual ↑ in IOP and progressive vision loss.
Risk factors	Family history, older age, **Asian,** hyperopia, prolonged **pupillary dilation** (prolonged time in a dark area, stress, medications), anterior uveitis, and lens dislocation.	Risk factors include age > **40 years, black, diabetes,** and **myopia.**
History/PE	Extreme, sudden-onset eye pain, blurred vision, headache, nausea, and vomiting. A hard, red eye is seen; the pupil is dilated and nonreactive to light.	Should be suspected in patients > 35 years of age who need **frequent lens changes** and have mild headaches, visual disturbances, and impaired adaptation to darkness; usually asymptomatic until late in the clinical course. Characterized by gradual loss of peripheral vision. **Cupping** of the optic nerve head is seen on funduscopic exam (see Figure 2.10-12).
Diagnosis	Diagnosis is based on clinical history and examination. Fixed pupil and hard, red eye.	Tonometry, ophthalmoscopic visualization of the optic nerve and cupping of optic disk, and visual field testing are most important.
Treatment	A **medical emergency** that can cause blindness. Treatment to ↓ IOP is as follows: Eyedrops (timolol, pilocarpine). Systemic medications (oral or IV acetazolamide, IV mannitol). **Laser peripheral iridotomy,** which creates a hole in the peripheral iris, is **curative** and can be performed prophylactically. Do not give any medications that cause pupillary dilation.	Treat with topical β-blockers (timolol, betaxolol) to ↓ aqueous humor production. Pilocarpine to ↑ aqueous outflow. Carbonic anhydrase inhibitors (acetazolamide) can also be used. If medication fails, laser trabeculoplasty or a trabeculectomy can improve aqueous drainage.

AGE-RELATED MACULAR DEGENERATION

More common among whites, women, smokers, and those with a family history.

History/PE

- Presents with **painless loss of central vision.** Early signs include distortion of straight lines.
- **Atrophic ("dry") macular degeneration:** Responsible for 80% of cases. Causes gradual vision loss.
- **Exudative or neovascular ("wet") macular degeneration:** Much less common, but associated with more rapid and severe vision damage.

Diagnosis

- **Atrophic ("dry") macular degeneration:** Funduscopy reveals drusen (accumulation of white/yellow extracellular material) and/or pigmentary changes.
- **Exudative or neovascular ("wet") macular degeneration:** Hemorrhage and subretinal fluid are present (see Figure 2.10-13).



FIGURE 2.10-13. Macular degeneration with evidence of drusen and fibrosis in the macula (Reproduced with permission from USMLE-Rx.com.)

KEY FACT

In the United States, macular degeneration is the leading cause of permanent bilateral visual loss in the elderly.

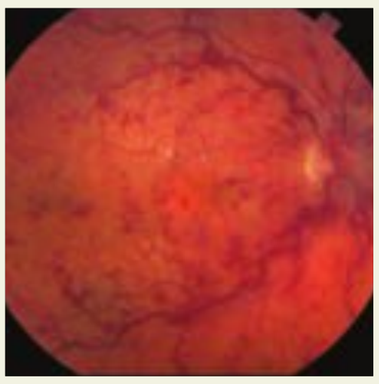
Treatment

- **Atrophic AMD:** No treatment is currently available, although a combination of vitamins (vitamin C, vitamin E, beta-carotene, and zinc) has been found to slow disease progression. Be cautious giving high doses of vitamin E and beta-carotene to patients who smoke as there is an association of ↑ mortality rate from lung cancer in people taking high doses of these supplements.
- **Exudative AMD:**
  - VEGF inhibitors have been shown to improve vision (ranibizumab, bevacizumab) or slow visual loss (pegaptanib) in patients with exudative AMD.
  - Photodynamic therapy using a laser to selectively target retinal vessels for coagulation. May be useful in conjunction with VEGF inhibitors.

RETINAL VASCULAR OCCLUSION

Occurs in **elderly patients** and is often idiopathic (see Table 2.10-16).

TABLE 2.10-16. Central Retinal Artery vs Central Retinal Vein Occlusion

	Central Retinal Artery Occlusion	Central Retinal Vein Occlusion
		
History/PE	Presents with sudden, **painless, unilateral blindness.** The pupil is sluggishly reactive to direct light. Patients present with a **cherry-red spot** on the fovea (blue arrow), retinal swelling (whitish appearance to the nerve fiber l yer), and retinal arteries that may appear bloodless.	Presents with rapid, **painless** vision loss of variable severity. Associated with hypertension. A swollen optic disk with hemorrhages, venous stasis retinal hemorrhages, cotton-wool spots, and macular edema may be seen on funduscopic exam.
Treatment	Ocular massage; intra-arterial thrombolysis within 8 hours.	Laser photocoagulation (variable results).

Central retinal artery occlusion image reproduced with permission from USMLE-Rx.com. Central retinal vein occlusion image reproduced with permission from Alasil T, Rauser ME. Intravitreal bevacizumab in the treatment of neovascular glaucoma secondary to central retinal vein occlusion: a case report, Cases J 2009 Oct 30;2:176.

HIGH-YIELD FACTS IN

OBSTETRICS

Physiology of Normal Pregnancy 296
- The Basics of Pregnancy 296
- diagnosis of Pregnancy 296
- Normal Physiology of Pregnancy 296

Prenatal Care 297

Prenatal Diagnostic Testing 299
- Quad Screening 300
- Pregnancy-Associated Plasma Protein A 300
- chorionic Villus Sampling 300
- Amniocentesis 301

Teratology 302

Maternal-Fetal Infections 302

Spontaneous Abortion 302

Elective Termination of Pregnancy 305

Normal Labor and Delivery 306
- obstetric Examination 306
- Fetal Heart Rate Monitoring 306
- Antepartum Fetal Surveillance 307
- obstetric Analgesia and Anesthesia 311

Medical Complications of Pregnancy 311
- Hyperemesis Gravidarum 311
- diabetes in Pregnancy 312
- Gestational and chronic Hypertension 313
- Preeclampsia and Eclampsia 314
- UTI and Pyelonephritis during Pregnancy 316
- Antepartum Hemorrhage 316

Obstetric Complications of Pregnancy 316
- Ectopic Pregnancy 316
- Intrauterine Growth Restriction 319
- Fetal Macrosomia 319
- Polyhydramnios 320
- oligohydramnios 320
- Rh Isoimmunization 320
- Gestational Trophoblastic disease 321
- Multiple Gestations 322

Abnormal Labor and Delivery 323
- Shoulder dystocia 323
- Failure to Progress 324
- Rupture of Membranes 324
- Preterm Labor 325
- Fetal Malpresentation 326
- Indications For cesarean Section 327
- Episiotomy 327

Puerperium 328
- Postpartum Hemorrhage 328
- Postpartum Infections 329
- Sheehan Syndrome (Postpartum Pituitary Necrosis) 329
- Lactation and Breastfeeding 329
- Mastitis 330

Physiology of Normal Pregnancy

THE BASICS OF PREGNANCY

The following terms and concepts are central to an understanding of the physiologic processes of pregnancy.

- **Gravidity:** The number of times a woman has been pregnant.
- **Parity:**
  - The number of pregnancies that led to a birth beyond 20 weeks' gestational age or an infant weighing > 500 g.
  - In prenatal assessment, P expresses the number of term deliveries, the number of preterm deliveries, the number of abortuses, and the number of living children (where P stands for "para").
- **Developmental age (DA):** The number of weeks and days since fertilization; usually unknown.
- **Gestational age (GA):** The number of weeks and days measured from the first day of the last menstrual period (LMP). GA can also be determined by:
  - **Fundal height:** Umbilicus – 20 weeks + 2–3 cm/week thereafter.
  - **Fetal heart tones (Doppler):** Typically 10–12 weeks.
  - **Quickening, or appreciation of fetal movement:** Occurs at 17–18 weeks at the earliest.
  - **Ultrasonography:**
    - Measures fetal crown-rump length (CRL) at 6–12 weeks.
    - Measures biparietal diameter (BPD), femur length (FL), and abdominal circumference (AC) from 13 weeks.
    - Ultrasound measurement of GA is most reliable during the first trimester.

KEY FACT

A G3P1 woman is one who has had three pregnancies but only one birth beyond 20 weeks' GA and/or an infant who weighs at least 500 g.

DIAGNOSIS OF PREGNANCY

β-hCG

KEY FACT

Get a quantitative β-hCG:

- To diagnose and follow ectopic pregnancy.
- To monitor trophoblastic disease.
- To screen for fetal aneuploidy.

- The standard for diagnosing pregnancy.
- Produced by the placenta; peaks at 100,000 mIU/mL by 10 weeks' GA.
- ↓ throughout the second trimester; levels off in the third trimester.
- **hCG levels double approximately every 48 hours during early pregnancy.** This is often used to diagnose ectopic pregnancy when doubling is abnormal.

Ultrasonography

- Used to confirm an intrauterine pregnancy.
- The gestational sac is visible on transvaginal ultrasonography by:
  - Five weeks' GA.
  - A β-hCG in the range of 1000–1500 mIU/mL.

NORMAL PHYSIOLOGY OF PREGNANCY

The normal physiologic changes that occur during pregnancy are graphically illustrated according to system in Figures 2.11-1 and 2.11-2.

SYSTEM	PARAMETER	PATTERN
Renal	Renal flow	Increases 25–50%.
	Glomular filtration rate	Increases early, then plateaus.
Weight	Uterine weight	Increases from about 60–70 g to about 900–1200 g.
	Body weight	Average 11-kg (25-lb) increase.

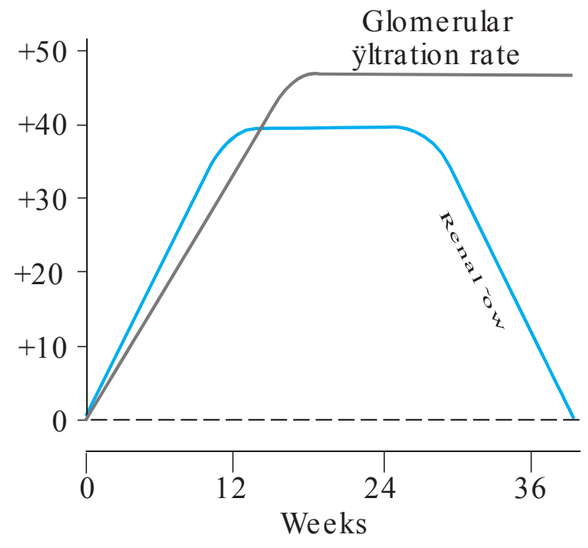


FIGURE 2.11-1. Renal and uterine/body weight changes in normal pregnancy. (Reproduced with permission from Gardner DG, Shoback D. Greenspan's Basic & Clinical Endocrinology, 8th ed. New York, NY: McGraw-Hill; 2007.)

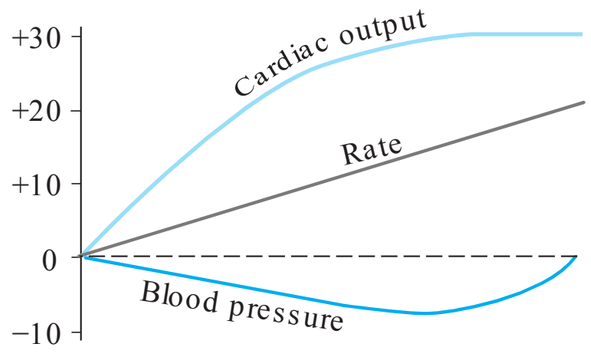
Prenatal Care

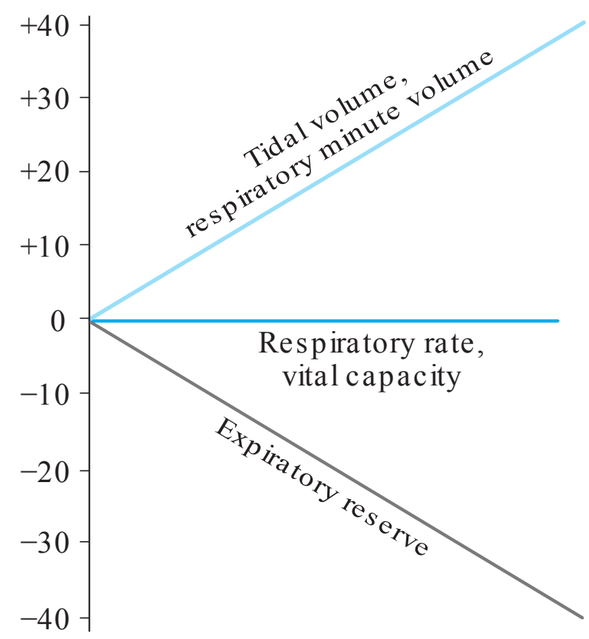
The goal of prenatal care is to prevent, diagnose, and treat conditions that can lead to adverse outcomes in pregnancy. Expected weight gain, nutrition, and exercise recommendations are outlined in Table 2.11-1. See Table 2.11-2 for some important factors that can cross the placenta.

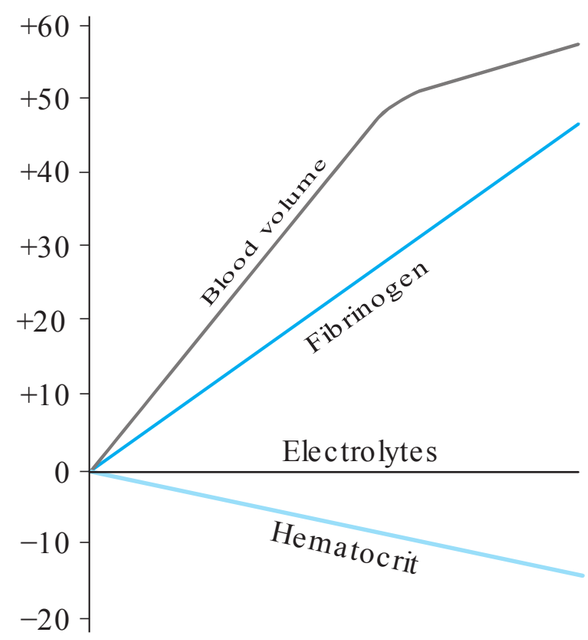
TABLE 2.11-1. Recommendations for Standard Prenatal Care

Category	Recommendations
Weight gain	Guidelines for weight gain in pregnancy: ▪ **Excessive gain:** > 1.5 kg/month. ▪ **Inadequate gain:** < 1.0 kg/month. Guidelines according to prepregnancy BMI: ▪ **Underweight** (BMI < 19.8): 12–18 kg. ▪ **Acceptable** (BMI 19.8–26.0): 11–16 kg. ▪ **Overweight** (BMI 26.1–29.0): 7–11 kg. ▪ **Severely overweight** (BMI > 29.0): 5–9 kg.
Nutrition	Guidelines for nutritional supplementation: ▪ An additional 100–300 kcal/day; 500 kcal/day during breastfeeding. ▪ **Folic acid supplements** (↓ neural tube defects for **all** reproductive-age women): 0.4 mg/day, or 4 mg/day for women with a history of neural tube defects in prior pregnancies. ▪ **Iron:** Starting at the first visi , 30 mg/day of elemental iron (or 150 mg of iron sulfate). ▪ **Calcium:** 1300 mg/day for women < 19 years of age; 1000 mg/day for those > 19 years of age. Additional guidelines for complete vegetarians: ▪ **Vitamin D:** 10 µg or 400 IU/day. ▪ **Vitamin B_{12}:** 2 µg/day.
Exercise	Thirty minutes of moderate exercise daily.

SYSTEM	PARAMETER	PATTERN
Cardiovascular	Heart rate	Gradually increases 20%.
	Blood pressure	Gradually decreases 10% by 34 weeks, then increases to prepregnancy values.
	Stroke volume	Increases to maximum at 19 weeks, then plateaus.
	Cardiac output	Rises rapidly by 20%, then gradually increases an additional 10% by 28 weeks.
	Peripheral venous distention	Progressive increase to term.
	Peripheral vascular resistance	Progressive decrease to term.
Pulmonary	Respiratory rate	Unchanged.
	Tidal volume	Increases by 30–40%.
	Expiratory reserve	Gradual decrease.
	Vital capacity	Unchanged.
	Respiratory minute volume	Increases by 40%.
Blood	Volume	Increases by 50% in second trimester.
	Hematocrit	Decreases slightly.
	Fibrinogen	Increases.
	Electrolytes	Unchanged.
Gastrointestinal	Sphincter tone	Decreases.
	Gastric emptying time	Increases.







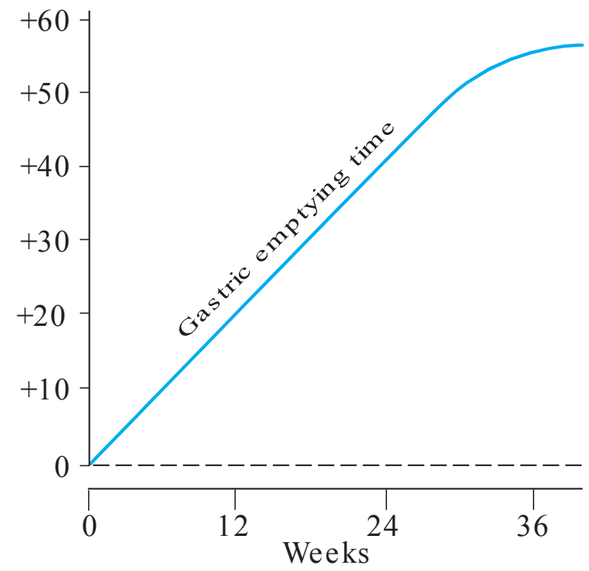


FIGURE 2.11-2. Cardiopulmonary, hematologic, and GI changes in normal pregnancy. (Reproduced with permission from Gardner DG, Shoback D. Greenspan's Basic & Clinical Endocrinology, 8th ed. New York, NY: McGraw-Hill; 2007.)

TABLE 2.11-2. Factors That Can Cross the Placenta

Immunoglobulins	Organisms	Drugs
IgG	Toxoplasma gondii Rubella HIV Varicella-zoster virus CMV Enteroviruses Treponema pallidum Listeria monocytogenes Parvovirus B19	See the teratology discussion below.

Prenatal Diagnostic Testing

Table 2.11-3 outlines a typical prenatal diagnostic testing schedule by week. The sections that follow describe each recommended screening modality.

TABLE 2.11-3. Prenatal Diagnostic Testing Schedule

Weeks	Prenatal diagnostic testing
Prenatal visits	**Weeks 0–28:** Every 4 weeks. **Weeks 29–35:** Every 2 weeks. **Weeks 36–birth:** Every week.
Initial visit	**Heme:** CBC, Rh factor, type and screen. **Infectious disease:** UA and culture, rubella antibody titer, HBsAg, RPR/VDRL, cervical gonorrhea and chlamydia, PPD, HIV, Pap smear (to check for dysplasia). Consider HCV and varicella based on history. **If indicated:** HbA_{1c}, sickle cell screening. **Discuss genetic screening:** Tay-Sachs disease, cystic fibrosis.
9–14 weeks	Offer PAPP-A + nuchal transparency + free β-hCG ± CVS.
15–22 weeks	Offer maternal serum α-fetoprotein (MSAFP) or quad screen (AFP, estriol, β-hCG, and inhibin A) ± amniocentesis.
18–20 weeks	Ultrasonography for full anatomic screen.
24–28 weeks	One-hour glucose challenge test for gestational diabetes screen.
28–30 weeks	RhoGAM for Rh-⊖ women (after antibody screen).
35–37 weeks	GBS culture; repeat CBC.
34–40 weeks	In high-risk patients, cervical chlamydia and gonorrhea cultures, HIV, RPR.

QUAD SCREENING

- **Quad screening** consists of the following four elements (see also Table 2.11-4):
  1. MSAFP
  2. Inhibin A
  3. Estriol
  4. β-hCG
- MSAFP is produced by the fetus and enters the maternal circulation. Results are reported as multiples of the median (MoMs).
  - Measurement results depend on accurate gestational dating.
  - MSAFP is rarely tested alone, as quad screening has ↑ sensitivity for detecting chromosomal abnormalities.
- **Elevated MSAFP (> 2.5 MoMs) is associated with:**
  - Open–neural tube defects (anencephaly, spina bifida).
  - Abdominal wall defects (gastroschisis, omphalocele).
  - Multiple gestation.
  - Incorrect gestational dating.
  - Fetal death.
  - Placental abnormalities (eg, placental abruption).
- **Reduced MSAFP (< 0.5 MoM) is associated with:**
  - Trisomy 21 and 18.
  - Fetal demise.
  - Incorrect gestational dating.

KEY FACT

Still **UNDER**age at **18:** trisomy **18** = ↓ AFP, ↓ estriol, ↓ β-hCG, ↓ inhibin A.

KEY FACT

2 up, 2 down: trisomy **21** = ↓ AFP, ↓ estriol, ↑ β-hCG, ↑ inhibin A.

PREGNANCY-ASSOCIATED PLASMA PROTEIN A

- Recommended at weeks 9–14.
- PAPP-A + nuchal transparency + free β-hCG can detect ~ 91% of cases of Down syndrome and ~ 95% of cases of trisomy 18.
- Advantages:
  - A screen of pregnant women (> 35 years of age).
  - Available earlier than CVS and less invasive than CVS (see below).

CHORIONIC VILLUS SAMPLING

Table 2.11-5 outlines the relative advantages and disadvantages of CVS and amniocentesis (see also Figure 2.11-3).

TABLE 2.11-4. Quad Screening

	MSAFP	Estriol	Inhibin A	β-hCG
Trisomy 18	↓	↓	↓	↓
Trisomy 21	↓	↓	↑	↑

TABLE 2.11-5. CVS vs Amniocentesis

Variable	CVS	Amniocentesis	Cell-Free Fetal DNA
GA	10–12 weeks.	15–20 weeks.	10 weeks.
Procedure	Transcervical or transabdominal aspiration of placental tissue.	Transabdominal aspiration of amniotic fluid using an ultrasound-guided needle.	Isolation of fetal DNA from blood sample obtained from mother.
Advantages	Genetically diagnostic. Available at an earlier GA.	Genetically diagnostic.	Noninvasive.
Disadvantages	Risk of fetal loss is relatively high (1%). Cannot detect open–neural tube defects. Limb defects are associated with CVS at < 9 weeks.	PROM, chorioamnionitis, fetal-maternal hemorrhage.	May be limited due to low concentration of fetal DNA in maternal circulation.

AMNIOCENTESIS

Indicated for the following:

- In women who will be > 35 years of age at the time of delivery.
- In conjunction with an abnormal quad screen.
- In Rh-sensitized pregnancy to obtain fetal blood type or to detect fetal hemolysis.
- To evaluate fetal lung maturity via a lecithin-to-sphingomyelin ratio ≥ 2.5 or to detect the presence of phosphatidylglycerol (performed during the third trimester).

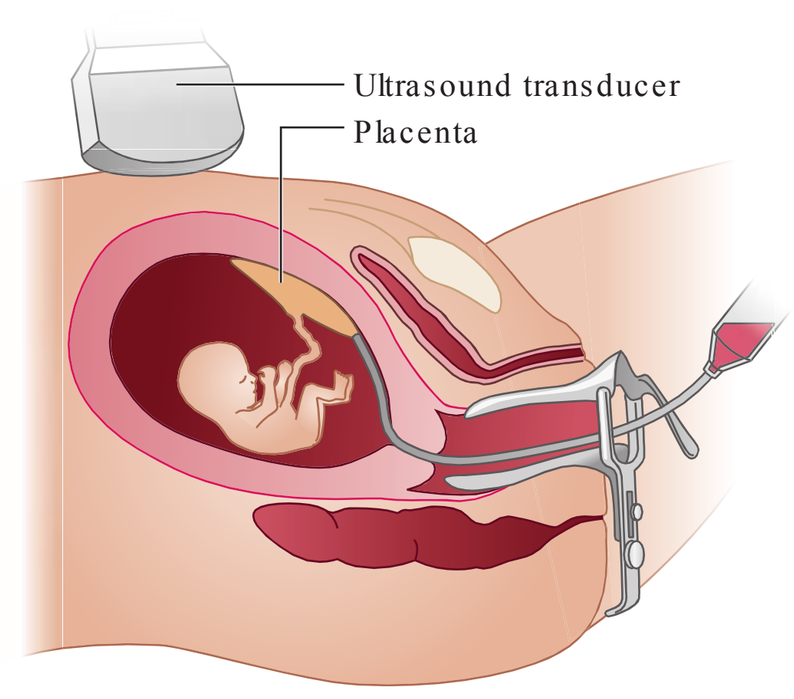


FIGURE 2.11-3. Chorionic villus sampling. (Reproduced with permission from Cunningham FG et al. Williams Obstetrics, 23rd ed. New York, NY: McGraw-Hill; 2010.)

Teratology

Major defects are apparent in about 3% of births and in roughly 4.5% of children by 5 years of age. Table 2.11-6 outlines common teratogenic agents.

MNEMONIC

TORCHeS pathogens—

Toxoplasmosis
Other[a]
Rubella
CMV
Herpes simplex virus
HIV
Syphilis

[a]Parvovirus, varicella, Listeria, TB, malaria, fungi.

KEY FACT

Pregnant women should not change the cat's litterbox.

Maternal-Fetal Infections

- Can occur at any time during pregnancy, labor, and delivery. Common sequelae include the following:
  - Premature delivery.
  - CNS abnormalities.
  - Anemia.
  - Jaundice.
  - Hepatosplenomegaly.
  - Growth retardation.
- The most common pathogens involved can be remembered through use of the **TORCHeS** mnemonic (see also Table 2.11-7).

Spontaneous Abortion

The loss of products of conception (POC) prior to the 20th week of pregnancy. More than 80% of cases occur in the first trimester. Risk factors are as follows:

- **Chromosomal abnormalities:** A factor in approximately 50% of SABs in the first trimester, 20–30% in second-trimester losses, and 5–10% in third-trimester losses.
- **Maternal factors:**
  - **Inherited thrombophilias:** Factor V Leiden, prothrombin, antithrombin, proteins C and S, methylene tetrahydrofolate reductase (hyperhomocysteinemia).
  - **Immunologic issues:** Antiphospholipid antibodies; alloimmune factors.
  - **Anatomic issues:** Uterine and cervical abnormalities, incompetent cervix, cervical conization or loop electrosurgical excision procedure (LEEP), cervical injury, DES exposure.
  - **Endocrinologic issues:** Diabetes mellitus (DM), hypothyroidism, progesterone deficiency.
  - **Other:** Maternal trauma, ↑ maternal age, infection, dietary deficiencies.
- **Environmental factors:** Tobacco, alcohol, caffeine (> 500 mg of caffeine per day), toxins, drugs, radiation.
- **Fetal factors:** Anatomic malformation.
- **Recurrent SAB: Two or more consecutive SABs or three SABs in 1 year, causes dependent on timing. To determine possible causes, karyotype both parents, hypercoagulability workup of mother, evaluate uterine anatomy.**
  - Early (< 12 weeks): Chromosomal abnormalities likely cause.
  - Late (12–20 weeks): Hypercoagulable states (eg, SLE, factor V Leiden, protein S deficiency).

KEY FACT

To remember the cervical exam during Inevitable and Incomplete SABs:
The **Is** are **Open**

HISTORY/PE

See Table 2.11-8 for types of SAB.

TABLE 2.11-6. Common Teratogenic Agents and Their Associated Defects

Drugs and Chemicals	Defects
ACEIs	Fetal renal tubular dysplasia and neonatal renal failure, oligohydramnios, IUGR, lack of cranial ossific tion.
Alcohol	Fetal alcohol syndrome (growth restriction before and after birth, mental retardation, midfacial hypoplasia, renal and cardiac defects). Consumption of > 6 drinks per day is associated with a 40% risk of fetal alcohol syndrome.
Androgens	Virilization of female fetuses; advanced genital development in male fetuses.
Carbamazepine	Neural tube defects, finge nail hypoplasia, microcephaly, developmental delay, IUGR.
Cocaine	Bowel atresias; congenital malformations of the heart, limbs, face, and GU tract; microcephaly; IUGR; cerebral infarctions.
DES	Clear cell adenocarcinoma of the vagina or cervix, vaginal adenosis, abnormalities of the cervix and uterus or testes, possible infertility.
Lead	↑ SAB rate; stillbirths.
Lithium	Congenital heart disease (Ebstein anomaly).
Methotrexate	↑ SAB rate.
Organic mercury	Cerebral atrophy, microcephaly, mental retardation, spasticity, seizures, blindness.
Phenytoin	IUGR, mental retardation, microcephaly, dysmorphic craniofacial features, cardiac defects, finge nail hypoplasia.
Radiation	Microcephaly, mental retardation. Medical diagnostic radiation delivering < 0.05 Gy to the fetus has no teratogenic risk.
Streptomycin and kanamycin	Hearing loss; CN VIII damage.
Tetracycline	Permanent yellow-brown discoloration of deciduous teeth; hypoplasia of tooth enamel.
Thalidomide	Bilateral limb deficiencie , anotia and microtia, cardiac and GI anomalies.
Trimethadione and paramethadione	Cleft lip or cleft palate, cardiac defects, microcephaly, mental retardation.
Valproic acid	Neural tube defects (spina bifida); minor c aniofacial defects.
Vitamin A and derivatives	↑ SAB rate, microtia, thymic agenesis, cardiovascular defects, craniofacial dysmorphism, microphthalmia, cleft lip or cleft palate, mental retardation.
Warfarin (wages **war** on the fetus)	Nasal hypoplasia and stippled bone epiphyses, developmental delay, IUGR, ophthalmologic abnormalities.

TABLE 2.11-7. Diagnosis and Treatment of Common Congenital Infections

Disease	Transmission	Symptoms	Diagnosis	Treatment	Prevention
Toxoplasmosis	Transplacental; 1° infection via consumption of raw meat or contact with cat feces.	Hydrocephalus. Intracranial calcifications. Chorioretinitis. Ring-enhancing lesions on MRI.	Serologic testing.	Pyrimethamine + sulfadiazine.	Avoid exposure to cat feces during pregnancy; spiramycin prophylaxis for the third trimester.
Rubella	Transplacental in the first trimester.	Purpuric "blueberry muffin" rash. Cataracts. Mental retardation. Hearing loss. PDA.	Serologic testing.	Symptomatic.	Immunize before pregnancy; vaccinate the mother after delivery if serologic titers remain ⊖.
CMV	Primarily transplacental.	Petechial rash. Periventricular calcifications.	Urine culture; PCR of amniotic fluid.	Postpartum ganciclovir.	N/A.
HSV	Intrapartum transmission if the mother has active lesions; transplacental transmission is rare.	Skin, eye, and mouth infections. Life-threatening CNS/systemic infection.	Serologic testing.	Acyclovir.	Perform a C-section if lesions are present at delivery.
HIV	In utero, at delivery, or via breast milk.	Often asymptomatic. Failure to thrive. Bacterial infections. ↑ incidence of upper and lower respiratory diseases.	ELISA, Western blot.	HAART.	AZT or nevirapine in pregnant women with HIV; perform elective C-section if viral load is > 1000. Treat infants with prophylactic AZT; avoid breastfeeding.
Syphilis	Intrapartum; transplacental transmission is possible.	Maculopapular skin rash. Lymphadenopathy. Hepatomegaly. "Snuffles": mucopurulent rhinitis. Osteitis. Late congenital syphilis: ▪ Saber shins. ▪ Saddle nose. ▪ CNS involvement. ▪ Hutchinson triad: peg-shaped central incisors, deafness, interstitial keratitis.	Dark-field microscopy, VDRL/RPR, FTA-ABS.	Penicillin.	Penicillin in pregnant women who test ⊕.

TABLE 2.11-8. Types of SAB

Type	Symptoms/Signs	Diagnosis	Treatment
Complete	**Bleeding and cramping stopped. POC expelled.**	**Closed os.** Ultrasonography shows no POC.	None.
Threatened	**Uterine** bleeding ± abdominal pain (often painless). **No POC expulsion.**	**Closed os** + intact membranes + fetal cardiac motion on ultrasonography.	Pelvic rest for 24–48 hours and follow-up ultrasonography to assess the viability of conceptus.
Incomplete	**Partial POC expulsion;** bleeding/ mild cramping. Visible tissue on exam.	**Open os.** POC present on ultrasonography.	Manual uterine aspiration (MUA) if < 12 weeks or D&C; may also use misoprostol or expectant management in inevitable and missed SABs.
Inevitable	Uterine bleeding and cramps. **No POC expulsion.**	**Open os** ± ROM. POC present on ultrasonography.	
Missed	**Cramping, loss of early pregnancy symptoms.** No bleeding.	**Closed os.** No fetal cardiac activity; POC present on ultrasonography.	
Septic	Foul-smelling discharge, abdominal pain, fever, and cervical motion tenderness; ± POC expulsion. Maternal mortality is 10–15%.	Hypotension, hypothermia, ↑ WBC count. Blood cultures.	MUA or D&C and IV antibiotics.
Intrauterine fetal demise	Absence of fetal cardiac activity > 20 weeks GA.	Uterus small for GA; no fetal heart tones or movement on ultrasonography.	Induce labor; evacuate the uterus (D&E) to prevent DIC at GA > 16 weeks.

Diagnosis/Treatment

- **Nonviable pregnancy:** Gestational sac > 25 mm without a fetal pole or absence of fetal cardiac activity when CRL > 7 mm on transvaginal ultrasonography.
- Clinical presentation, speculum exam, ultrasonography and serum β-hCG.
- Ultrasonography can identify:
  - The gestational sac 5–6 weeks from the LMP.
  - The fetal pole at 6 weeks.
  - Fetal cardiac activity at 6–7 weeks.
- See Table 2.11-8 for treatment specific to the type of SAB.
- Administer RhoGAM if the mother is Rh ⊖.

Elective Termination of Pregnancy

It has been estimated that 50% of all pregnancies in the United States are unintended. Some 25% of all pregnancies end in elective abortion. Options for elective abortion depend on GA and patient preferences (see Table 2.11-9).

Q

A 23-year-old G1P0 woman at 15 weeks GA presents with abdominal pain and mild bleeding from the cervix. On pelvic examination, some POC are found to be present in the vaginal vault. What test is necessary to determine the next step in management?

TABLE 2.11-9. Elective Termination of Pregnancy

Trimester	Procedure	Timing
First (90% TABs)	**Medical management:** ▪ Oral mifepristone (low dose) + oral/vaginal misoprostol. ▪ IM/oral methotrexate + oral/vaginal misoprostol. ▪ Vaginal or sublingual or buccal misoprostol (high dose), repeated up to 3 times. **Surgical management:** ▪ Manual uterine aspiration (MUA). ▪ D&C with vacuum aspiration.	**Up to:** 49 days GA 49 days GA 59 days GA 13 weeks GA
Second (10% TABs)	**Obstetric management:** Induction of labor (typically with prostaglandins, amniotomy, and oxytocin). **Surgical management:** D&E.	13–24 weeks GA (depending on state laws). Same as above.

Normal Labor and Delivery

OBSTETRIC EXAMINATION

- Leopold maneuvers are used to determine fetal lie (longitudinal or transverse) and, if possible, fetal presentation (breech or cephalic).
- **Cervical examination:**
  - Evaluate dilation, effacement, station, cervical position, and cervical consistency.
  - Confirm or determine fetal presentation.
  - Determine fetal position through palpation of the fetal sutures and fontanelles.
  - **Conduct a sterile speculum exam if ROM is suspected.**
  - Determine station, or engagement of the fetal head relative to a line through the ischial spines of the maternal pelvis. ⊖ station = fetal head superior to this line; ⊕ station = fetal head inferior to this line.
- Table 2.11-10 depicts the normal stages of labor.

FETAL HEART RATE MONITORING

- Monitoring can be performed with an electrode attached to the fetal scalp (a method that yields more precise results), or external monitoring can be conducted using Doppler ultrasound (a less invasive option).
- Continuous electronic FHR monitoring has not been shown to be more effective than appropriate intermittent monitoring in low-risk patients.

Recommendations for FHR Monitoring

- **Patients without complications:** Review FHR tracings.
  - **First stage of labor:** Every 30 minutes.
  - **Second stage of labor:** Every 15 minutes.

A

Ultrasonography should be performed to determine if all the POC have been expelled (ie, if the uterus is empty). If so, it is a complete abortion and the POC should be sent to pathology to confirm fetal tissue with no other treatment. If POC are retained, it is an incomplete abortion, and manual uterine aspiration or D&C is indicated. Medical management with misoprostol may also be appropriate.

TABLE 2.11-10. Stages of Labor

Stage	Starts/ends	duration: primiparous	duration: multiparous	comments
First				
Latent	Onset of labor to 3–4 cm dilation.	6–11 hours	4–8 hours	Prolongation seen with excessive sedation/ hypotonic uterine contractions.
Active	4 cm to complete cervical dilation (10 cm).	4–6 hours (1.2 cm/hour)	2–3 hours (1.5 cm/hour)	Prolongation seen with cephalopelvic disproportion.
Second	Complete cervical dilation to delivery of infant.	0.5–3.0 hours	5–30 minutes	Neonate goes through all cardinal movements of delivery.
Third	Delivery of infant to delivery of placenta.	0–0.5 hour	0–0.5 hour	Uterus contracts and placenta separates to establish hemostasis.

- **Patients with complications:** Review FHR tracings.
  - **First stage of labor:** Every 15 minutes.
  - **Second stage of labor:** Every 5 minutes.

Components of FHR Evaluation

- **Rate** (normal = 110–160 bpm):
  - **FHR < 110 bpm:** Bradycardia. Can be caused by congenital heart malformations or by severe hypoxia (2° to uterine hyperstimulation, cord prolapse, or rapid fetal descent).
  - **FHR > 160 bpm:** Tachycardia. Causes include hypoxia, maternal fever, and fetal anemia.
- **Variability:** See Figures 2.11-4 and 2.11-5.
  - **Absent variability:** Indicates severe fetal distress.
  - **Minimal variability:** < 6 bpm. Indicates fetal hypoxia or the effects of opioids, magnesium, or sleep cycle.
  - **Normal variability:** 6–25 bpm.
  - **Marked variability:** > 25 bpm. May indicate fetal hypoxia; may occur before a ↓ in variability.
  - **Sinusoidal variability:** Points to serious fetal anemia; a pseudosinusoidal pattern may also occur during maternal meperidine use.
- **Accelerations:** Onset of an ↑ in FHR > 15 beats above baseline to a peak in < 30 seconds. Reassuring because they indicate fetal ability to appropriately respond to the environment.
- **Decelerations:** See Table 2.11-11.

ANTEPARTUM FETAL SURVEILLANCE

In general, antepartum fetal surveillance is used in pregnancies in which the risk of antepartum fetal demise is ↑. Testing is initiated in most at-risk patients at 32–34 weeks (or 26–28 weeks if there are multiple worrisome risk factors present). The following assessments are made:

- **Fetal movement assessment:**
  - Assessed by the mother as the number of fetal movements over 1 hour.
  - The average time to obtain 10 movements is up to 2 hours.
  - Maternal reports of ↓ fetal movements should be evaluated by means of the tests described below.

Q

A 17-year-old G1P0 girl with a history of genital HSV presents at 37 weeks in labor. What is the appropriate management of the patient at delivery?

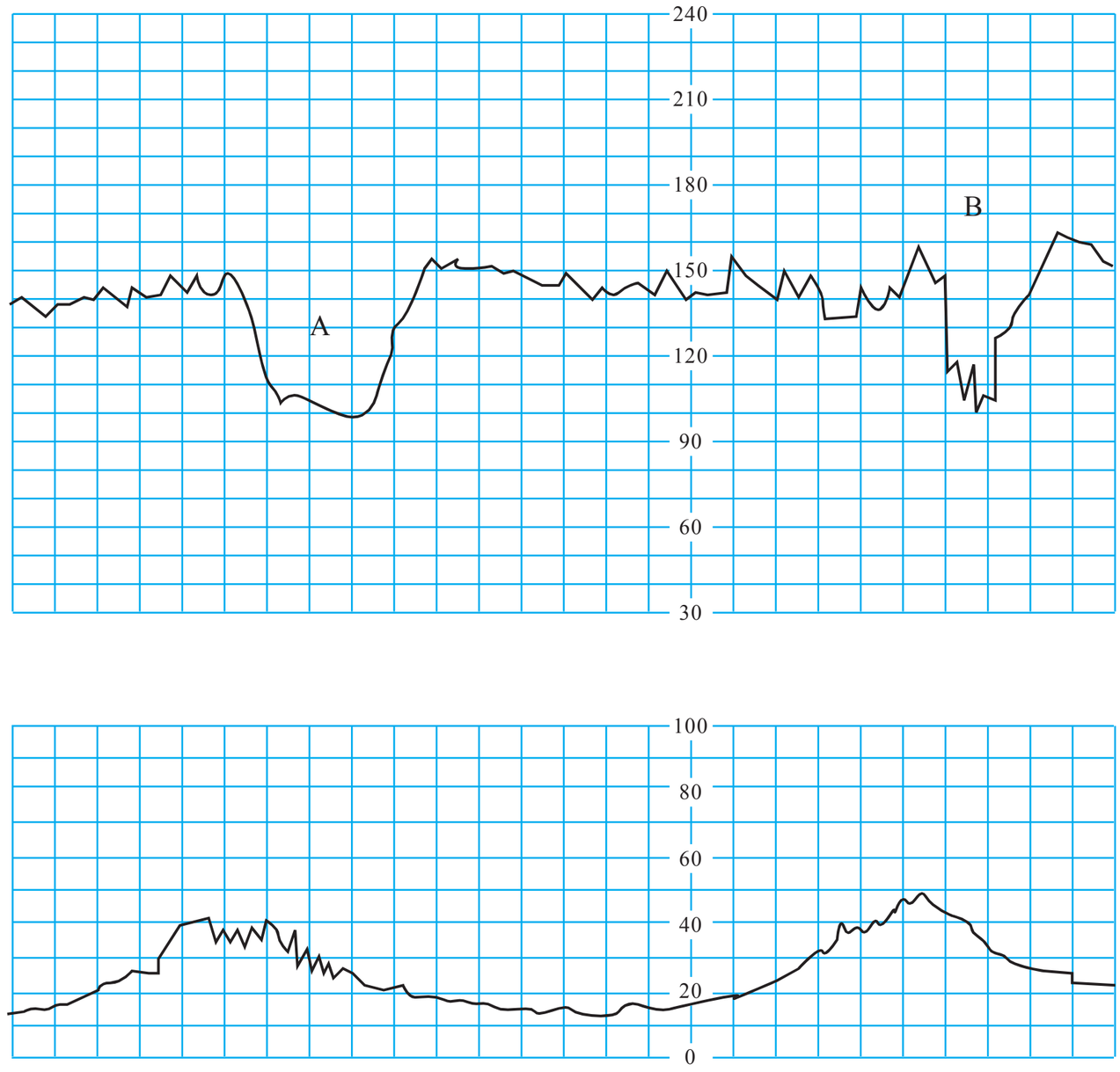


FIGURE 2.11-4. Varying (variable) fetal heart rate decelerations.

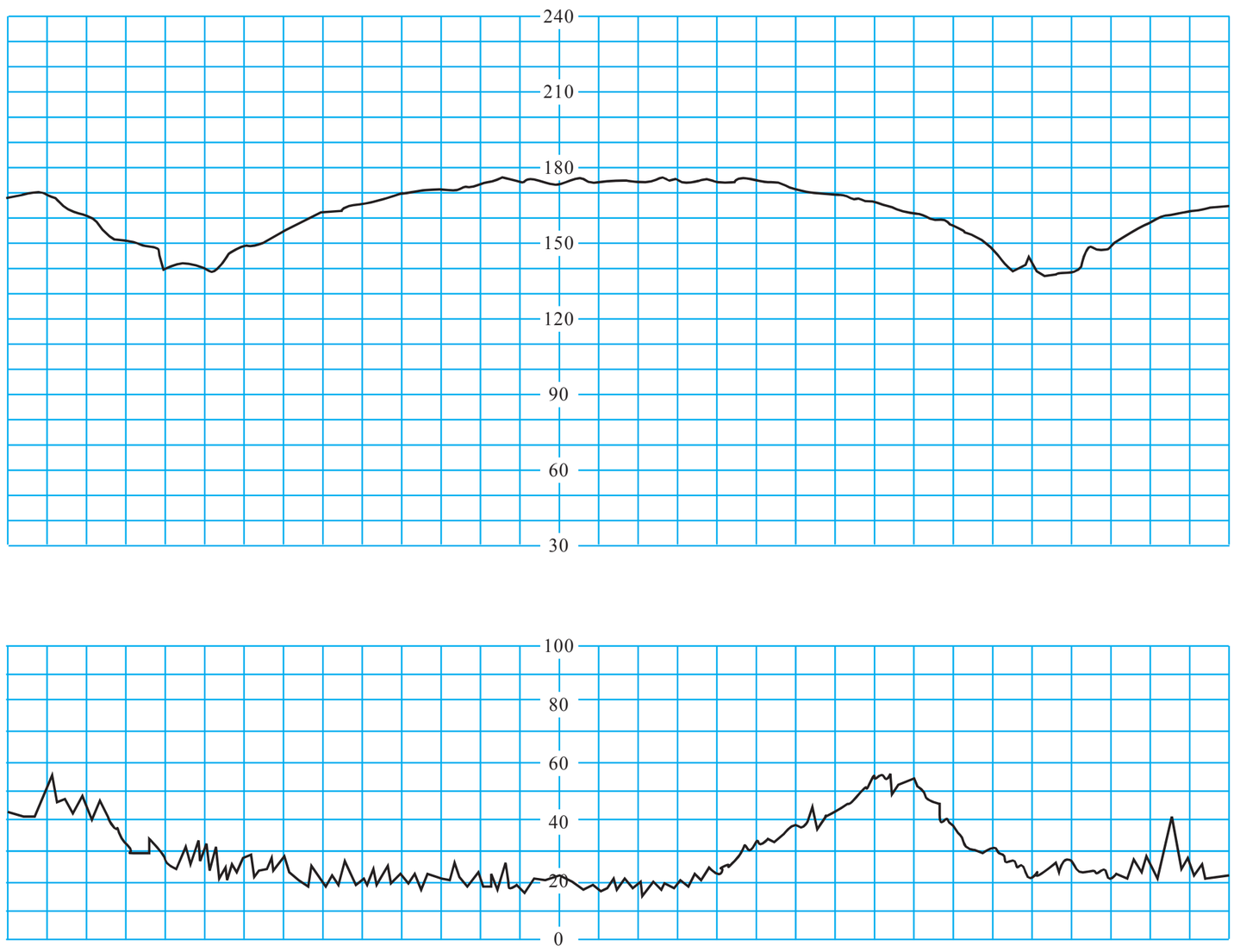
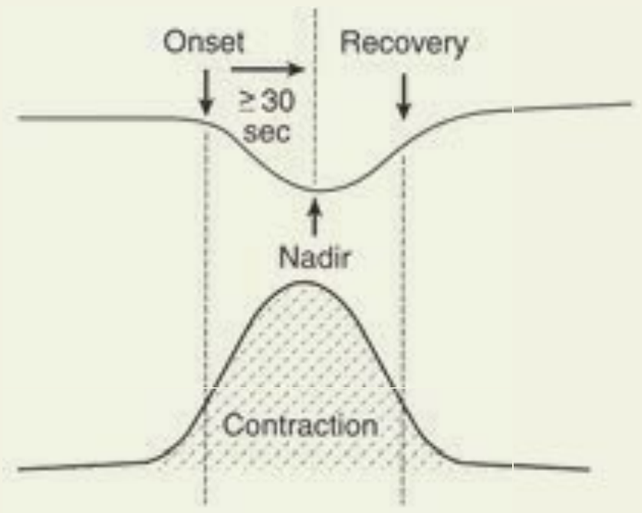
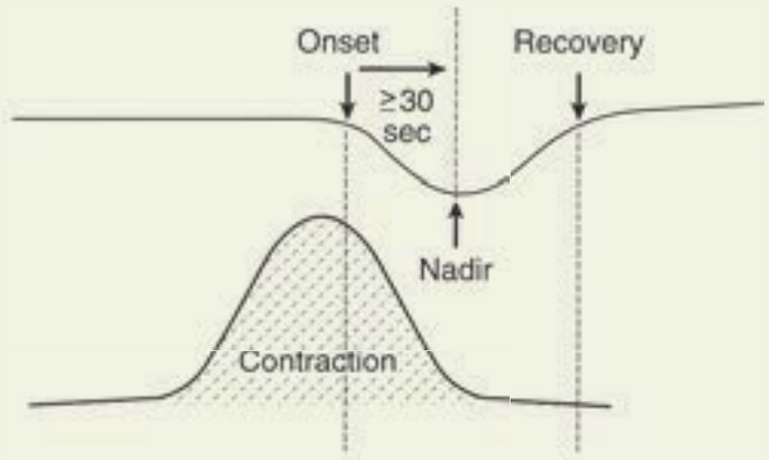
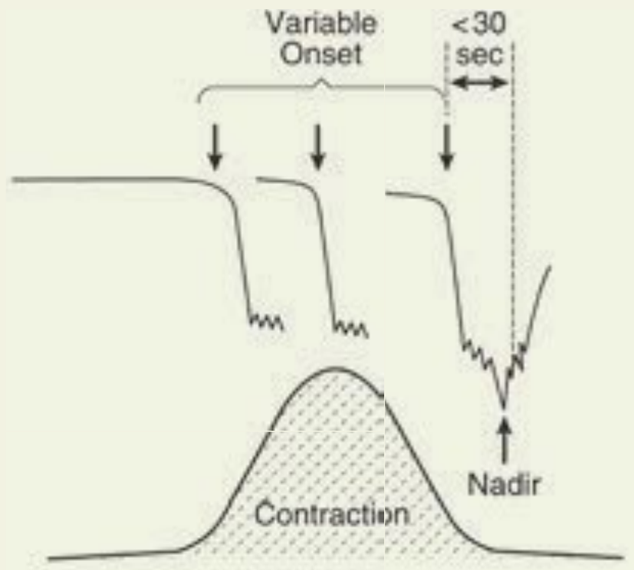


FIGURE 2.11-5. Late fetal heart rate decelerations. Late decelerations due to uteroplacental insufficiency resulting from placental abruption. Immediate cesarean delivery was performed. Umbilical artery pH was 7.05 and P_{O_2} was 11 mm Hg. (Adapted with permission from Cunningham FG et al. Williams Obstetrics, 23rd ed. New York, NY: McGraw-Hill; 2010.)

A

If the patient has any active lesions at the time of delivery, perform a C-section.

TABLE 2.11-11. Types of Fetal Deceleration

type	description	etiology	schematic
Early	A visually apparent, gradual (onset to nadir in > 30 seconds) ↓ in FHR with a return to baseline that mirrors the uterine contraction.	Head compression from the uterine contraction (normal).	
Late	A visually apparent, gradual (onset to nadir in > 30 seconds) ↓ in FHR with return to baseline whose onset, nadir, and recovery occur after the beginning, peak, and end of uterine contraction, respectively.	Uteroplacental insufficiency and fetal hypoxemia.	
Variable	An abrupt (onset to nadir in < 30 seconds), visually apparent ↓ in FHR 15 bpm below baseline lasting ≥ 15 seconds but < 2 minutes.	Umbilical cord compression.	

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- **Nonstress test (NST):**
  - Performed with the mother resting in the lateral tilt position (to prevent supine hypotension).
  - FHR is monitored externally by Doppler along with a tocodynamometer to detect uterine contractions. Acoustic stimulation may be used.
  - **"Reactive" NST (normal response):** Two accelerations ≥ **15 bpm above baseline** (if > 32 weeks GA; ≥ 10 bpm if < 32 weeks GA) **lasting for at least 15 seconds** over a 20-minute period (see Figure 2.11-6).
  - **"Nonreactive" NST:** Insufficient accelerations over a 40-minute period.
    - Perform further tests (eg, a biophysical profile, or BPP).
    - Lack of FHR accelerations may occur with any of the following: GA < 32 weeks, fetal sleeping, fetal CNS anomalies, and maternal sedative or narcotic administration.

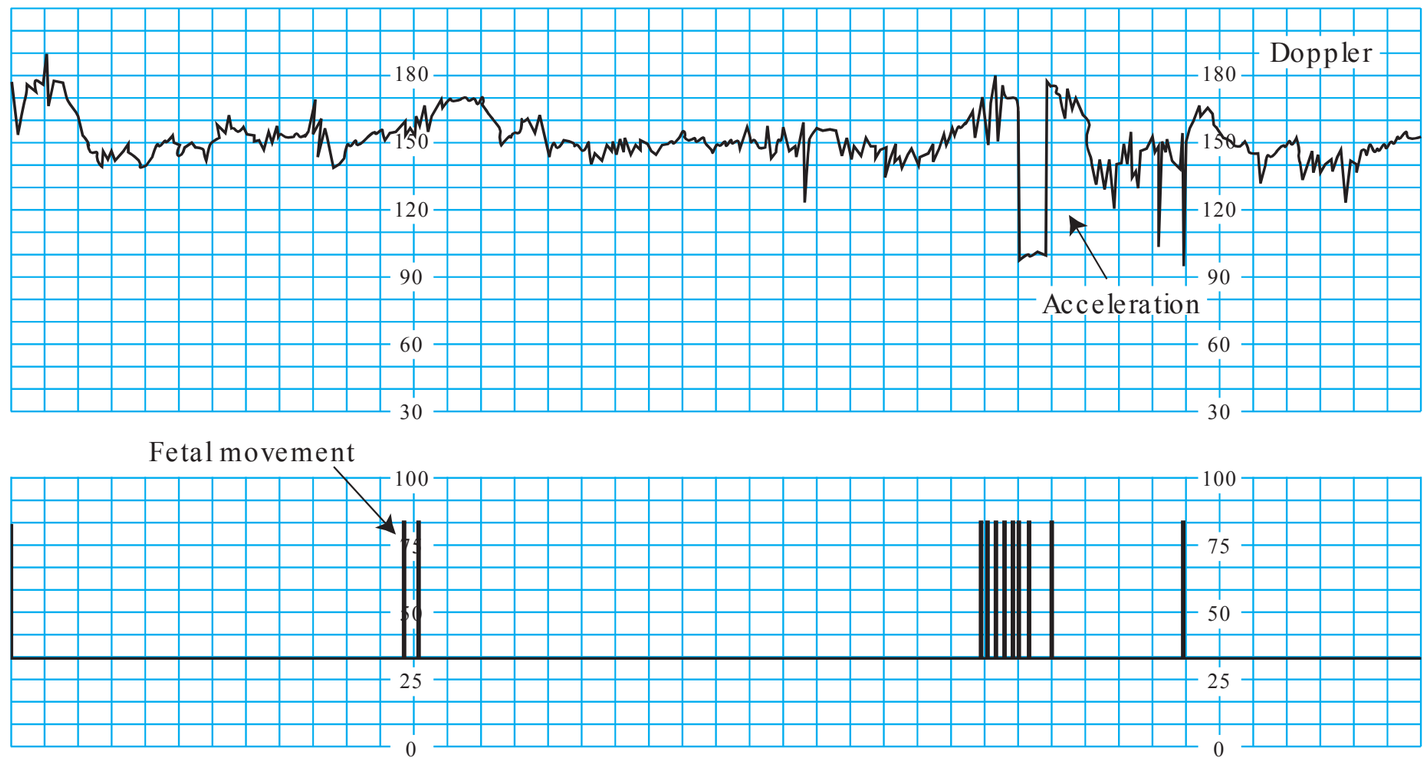


FIGURE 2.11-6. Reactive nonstress test. (Adapted with permission from Cunningham FG et al. Williams Obstetrics, 23rd ed. New York, NY: McGraw-Hill; 2010.)

- **Contraction stress test (CST):**
  - Performed in the lateral recumbent position.
  - FHR is monitored during spontaneous or induced (via nipple stimulation or oxytocin) contractions.
  - Reactivity is determined from fetal heart monitoring, as with the NST.
  - The procedure is contraindicated in women with preterm membrane rupture or known placenta previa; those with a history of uterine surgery; and those who are at high risk for preterm labor.
  - **"Positive" CST:**
    - Defined by late decelerations following 50% or more of contractions in a 10-minute window.
    - Raises concerns about fetal compromise.
    - Delivery is usually warranted.
  - **"Negative" CST:**
    - Defined as no late or significant variable decelerations within 10 minutes and at least three contractions.
    - Highly predictive of fetal well-being in conjunction with a normal NST.
  - **"Equivocal" CST:** Defined by intermittent late decelerations or significant variable decelerations.
- **Biophysical Profile (BPP):** Uses real-time ultrasonography to assign a score of 2 (normal) or 0 (abnormal) to five parameters: fetal tone, breathing, movement, amniotic fluid volume, and NST. Scoring is as follows:
  - **8–10:** Reassuring for fetal well-being.
  - **6:** Considered equivocal. Term pregnancies are usually delivered with this profile.
  - **0–4:** Extremely worrisome for fetal asphyxia; strong consideration should be given to immediate delivery if no other explanation is found.
- **Amniotic fluid index (AFI):** Sum of the measurements of the deepest cord-free amniotic fluid measured in each of the abdominal quadrants.
- **Modified biophysical profile (mBPP):**
  - NST + AFI.
  - A normal test consists of a reactive NST and an AFI > 5 cm.

KEY FACT

A ⊖ CST is good; a ⊕ one is bad.

MNEMONIC

When performing a BPP, remember to—

Test the Baby, MAN!

Fetal **T**one
Fetal **B**reathing
Fetal **M**ovement
Amniotic fluid olume
Nonstress test

- **Umbilical artery Doppler velocimetry:**
  - Used only when IUGR is suspected.
  - With IUGR, there is a reduction and even a reversal of umbilical artery diastolic flow.
- **Oligohydramnios (AFI < 5 cm) always warrants further workup.**

OBSTETRIC ANALGESIA AND ANESTHESIA

- Uterine contractions and cervical dilation result in visceral pain (T10–L1).
- Descent of the fetal head and pressure on the vagina and perineum result in somatic pain (pudendal nerve, S2–S4).
- In the absence of a medical contraindication, maternal request is a sufficient medical indication for pain relief during labor.
- Absolute contraindications to regional anesthesia (epidural, spinal, or combination) include the following:
  - Refractory maternal hypotension.
  - Maternal coagulopathy.
  - Maternal use of a once-daily dose of low-molecular-weight heparin within 12 hours.
  - Untreated maternal bacteremia.
  - Skin infection over the site of needle placement.
  - ↑ ICP caused by a mass lesion.

Medical Complications of Pregnancy

HYPEREMESIS GRAVIDARUM

Persistent vomiting not related to other causes, **acute starvation** (usually large ketonuria), and weight loss (usually at least a 5% ↓ from prepregnancy weight).

- More common in first pregnancies, multiple gestations, and molar pregnancies.
- ↑ β-hCG and ↑ estradiol have been implicated in its pathophysiology.

History/PE

Distinguish from "morning sickness" (which usually starts between weeks 4 and 7 of pregnancy and resolves prior to 16 weeks, but can occur throughout pregnancy), acid reflux, gastroenteritis, hyperthyroidism, and neurologic conditions.

Diagnosis

- Check β-hCG level and perform ultrasonography to rule out molar pregnancy.
- Evaluate for ketonemia, ketonuria, hyponatremia, and hypokalemic, hypochloremic metabolic alkalosis. Measure liver enzymes, serum bilirubin, and serum amylase/lipase.

Treatment

- Administer vitamin B_6.
- Doxylamine (an antihistamine) PO.
- Promethazine or dimenhydrinate PO or rectal administration.
- **If severe:** Metoclopramide, ondansetron, prochlorperazine, or promethazine IM/PO.
- **If dehydrated:** IV fluids, IV nutritional supplementation, and dimenhydrinate IV.

KEY FACT

If "morning sickness" persists after the first trimester, think hyperemesis gravidarum.

KEY FACT

The first step in the diagnosis of hyperemesis gravidarum is to **rule out molar pregnancy** with ultrasound ± β-hCG.

DIABETES IN PREGNANCY

Diabetes in pregnancy is divided into two categories:

- **Gestational diabetes mellitus (GDM):** Onset occurs during pregnancy.
- **Pregestational:** Onset is prior to pregnancy. If the woman has risk factors for DM, **screen with fasting glucose or HbA_{1c}**; eg, BMI > 25 kg/m^2 (> 23 kg/m^2 for Asians), first-degree relative with DM, high-risk ethnicity (black, Asian, Hispanic, Pacific Islander, Native American), polycystic ovary syndrome, prior delivery of baby > 4.1 kg (9 lb) or Dx of GDM, hypertension or on Tx for hypertension, previous HbA_{1c} > 5.7% or impaired glucose tolerance or impaired fasting glucose, or HDL-C < 35 mg/dL or triglycerides > 250 mg/dL.

Gestational Diabetes Mellitus

Carbohydrate intolerance of variable severity that is first diagnosed during pregnancy. Occurs in 3–5% of all pregnancies, usually diagnosed in the third trimester (24–28 weeks).

History/PE

- Typically asymptomatic.
- May present with edema, polyhydramnios, or a large-for-GA infant (> 90th percentile).

Diagnosis

- **Screen with a 1-hour 50-g glucose challenge test:**
  - Venous plasma glucose is measured 1 hour later.
  - **Performed at 24–28 weeks.**
  - Values ≥ 140 mg/dL are considered abnormal.
- **Confirm with an oral 3-hour (100-g) glucose tolerance test (GTT)** showing any two of the following:
  - **Fasting:** > 95 mg/dL.
  - **1 hour:** > 180 mg/dL.
  - **2 hours:** > 155 mg/dL.
  - **3 hours:** > 140 mg/dL.

KEY FACT

Keys to the management of gestational diabetes: (1) the ADA diet; (2) insulin if needed; (3) ultrasonography for fetal growth; and (4) NST beginning at 34 weeks if requiring insulin or an oral hypoglycemic.

Treatment

- **Mother:**
  - Start with the **ADA diet,** regular exercise, and strict glucose monitoring (four times a day).
  - Tight maternal glucose control (fasting ≤ 95 mg/dL; 1 hour postprandial ≤ 140 mg/dL and 2-hour postprandial ≤ 120 mg/dL) improves outcomes.
  - Add insulin if dietary control is insufficient.
  - Give intrapartum insulin and dextrose to maintain tight control during delivery.
- **Fetus:**
  - Obtain periodic ultrasonography and NSTs to assess fetal growth and well-being.
  - It may be necessary to induce labor at 39–40 weeks in patients poorly controlled on insulin or an oral hypoglycemic agent.

Complications

More than 50% of patients go on to **develop glucose intolerance and/or type 2 DM** later in life. At 6–12 weeks postpartum, screen for DM (75 g 2-hour GTT) and repeat testing every 3 years if normal results.

Pregestational Diabetes and Pregnancy

Observed in 1% of all pregnancies. Insulin requirements may ↑ as much as threefold. Poorly controlled DM is associated with an ↑ **risk of congenital malformations,** fetal loss, and maternal/fetal morbidity during labor and delivery.

KEY FACT

Greater than 8, investigate! If HbA_{1c} is > 8%, look for congenital abnormalities.

Treatment

- **Mother:**
  - Renal, ophthalmologic, neural tube, and cardiac evaluation to assess for end-organ damage.
  - Strict glucose control (diet, exercise, insulin therapy, and frequent self-monitoring) to minimize fetal defects. **Fasting morning:** ≤ 95 mg/dL.
    - 1-hour postprandial: < 140 mg/dL.
    - **2-hour postprandial:** < 120 mg/dL.
    - Overnight glucose 60–99 mg/dL.
- **Fetus:**
  - **16–24 weeks:**
    - Quad screen for developmental anomalies (16–18 weeks).
    - Ultrasonography to determine fetal age and growth (18–20 weeks).
    - Fetal echo to evaluate for cardiac anomalies (22–24 weeks).
  - **32–34 weeks:**
    - Close fetal surveillance (eg, NST, CST, BPP). (If poor glucose control or small vessel disease, start at 26 weeks).
    - Admit if maternal DM has been poorly controlled or fetal parameters are a concern.
    - Serial ultrasonograms for fetal growth.
  - **Delivery and postpartum:**
    - Maintain normoglycemia (80–100 mg/dL) during labor with an IV insulin drip and hourly glucose measurements.
    - Consider early delivery in the setting of poor maternal glucose control, preeclampsia, macrosomia, or evidence of fetal lung maturity.
    - Cesarean delivery should be considered in the setting of an estimated fetal weight (EFW) > 4500 g.
    - Encourage breastfeeding with an appropriate ↑ in caloric intake.

KEY FACT

If UA before 20 weeks reveals glycosuria, think pregestational diabetes.

KEY FACT

Hyperglycemia in the first trimester suggests preexisting diabetes and should be managed as pregestational diabetes.

Complications

See Table 2.11-12.

GESTATIONAL AND CHRONIC HYPERTENSION

Defined as follows:

- **Gestational hypertension:**
  - Idiopathic hypertension without significant proteinuria (< 300 mg/L).
  - **Develops at > 20 weeks GA.**
  - As many as 25% of patients may go on to develop preeclampsia.
- **Chronic hypertension:**
  - Present before conception and at < 20 weeks GA.
  - May persist for > 12 weeks postpartum.
  - Up to one-third of patients may develop superimposed preeclampsia.

TABLE 2.11-12. Complications of Pregestational Diabetes Mellitus

Maternal Complications	Fetal Complications
DKA (type 1) or hyperglycemic hyperosmolar nonketotic coma (type 2).	Macrosomia or IUGR.
Preeclampsia/eclampsia.	Cardiac and renal defects.
Cephalopelvic disproportion (from macrosomia) and need for C-section.	Neural tube defects (eg, sacral agenesis).
Preterm labor.	Hypocalcemia.
Infection.	Polycythemia.
Polyhydramnios.	Hyperbilirubinemia.
Postpartum hemorrhage.	Hypoglycemia from hyperinsulinemia.
Maternal mortality.	RDS.
	Birth injury (eg, shoulder dystocia).
	Perinatal mortality.

Treatment

- Monitor BP closely.
- Treat with appropriate antihypertensives (eg, methyldopa, labetalol, nifedipine).
- **Do not give angiotensin-converting enzyme inhibitors (ACEIs) or diuretics.**
  - ACEIs are known to lead to uterine ischemia.
  - Diuretics can aggravate low plasma volume to the point of uterine ischemia.

MNEMONIC

The classic triad of preeclampsia—

It's not just HyPE

Hypertension
Proteinuria
Edema

Complications

Similar to those of preeclampsia (see below).

PREECLAMPSIA AND ECLAMPSIA

Distinguished as follows:

- **Preeclampsia:**
  - New-onset hypertension (systolic BP ≥ 140 mm Hg or diastolic BP ≥ 90 mm Hg) **and**
  - Proteinuria (> 300 mg of protein in a 24-hour period) occurring at > 20 weeks GA.
- **Eclampsia:** New-onset grand mal seizures in women with preeclampsia.
- **HELLP syndrome:** A variant of preeclampsia with a poor prognosis.
  - Consists of hemolytic anemia, elevated liver enzymes, and low platelets (see mnemonic).
  - The etiology is unknown, but clinical manifestations are explained by vasospasm leading to hemorrhage and organ necrosis.
  - Risk factors include nulliparity, black, extremes of age (< 20 or > 35 years), multiple gestation, molar pregnancy, renal disease (due to SLE or type 1 DM), a family history of preeclampsia, and chronic hypertension.

MNEMONIC

HELLP syndrome—

Hemolysis
Elevated **L**FTs
Low **P**latelets

History/Pe

See Table 2.11-13 for the signs and symptoms of preeclampsia and eclampsia.

TABLE 2.11-13. Presentation of Preeclampsia and Eclampsia

Disease Severity	Signs and Symptoms
Mild preeclampsia	Usually asymptomatic. BP ≥ **140/90 mm Hg** on two occasions > 6 hours apart. Proteinuria (> 300 mg/24 hours or 1 to 2 ⊕ urine dipsticks). Edema.
Severe preeclampsia	BP > **160/110 mm Hg** on two occasions > 6 hours apart. **Renal: Proteinuria** (> 5 g/24 hours or 3 to 4 ⊕ urine dipsticks) or oliguria (< 500 mL/24 hours). **Cerebral changes: Headache,** somnolence. **Visual changes: Blurred vision,** scotomata. **Other:** Hyperactive reflexes/clonus; **RUQ pain;** hemolysis, elevated liver enzymes, thrombocytopenia (HELLP syndrome).
Eclampsia	The most common signs preceding an eclamptic attack are **headache, visual changes,** and **RUQ/epigastric pain.** Seizures are severe if not controlled with anticonvulsant therapy.

Treatment

The only cure for preeclampsia/eclampsia is delivery of the fetus.

- **Preeclampsia:**
  - **Close to term or worsening preeclampsia:** Induce delivery with IV oxytocin, prostaglandin, or amniotomy.
  - **Far from term:** Treat with modified bed rest and expectant management.
  - **Prevent intrapartum seizures with a continuous magnesium sulfate drip.**
    - Watch for signs of magnesium toxicity (loss of DTRs, respiratory paralysis, coma).
    - Continue seizure prophylaxis for 24 hours postpartum.
    - Treat magnesium toxicity with IV calcium gluconate.
- **Severe preeclampsia:**
  - **Control BP** with labetalol and/or hydralazine (goal < 160/110 mm Hg with a diastolic BP of 90–100 mm Hg to maintain fetal blood flow).
  - **Continuous magnesium sulfate drip.**
  - **Deliver** by induction or C-section when the mother is stable.
- **Eclampsia:**
  - ABCs with supplemental O_2.
  - Seizure control/prophylaxis with **magnesium.**
    - If seizures recur, give IV diazepam.
    - Monitor for clinical magnesium toxicity; no need to routinely monitor magnesium blood levels if renal function is normal.
    - Monitor fetal status.
    - Control BP (labetalol and/or hydralazine).
    - Limit fluids; Foley catheter for strict I/Os.
  - Initiate delivery if the patient is stable and convulsions are controlled.
  - Postpartum management is the same as that for preeclampsia.
  - Seizures may occur antepartum (25%), intrapartum (50%), or postpartum (25%); most occur within 48 hours after delivery.

KEY FACT

Signs of severe preeclampsia are persistent headache or other cerebral or visual disturbances, persistent epigastric pain, and hyperreactive reflexes.

Q

A 36-year-old G1P0 woman with a history of SLE at 36 weeks GA presents with headache and RUQ pain. She is admitted and found to have a BP of 165/100 and 170/105 mm Hg when tested twice 6 hours apart, as well as 3+ protein on urine dipstick. Once her BP has been controlled with labetalol, what are the next steps in management?

Complications

- **Preeclampsia:** Prematurity, fetal distress, stillbirth, placental abruption, seizure, DIC, cerebral hemorrhage, serous retinal detachment, fetal/maternal death.
- **Eclampsia:** Cerebral hemorrhage, aspiration pneumonia, hypoxic encephalopathy, thromboembolic events, fetal/maternal death.

UTI AND PYELONEPHRITIS DURING PREGNANCY

Asymptomatic bacteriuria occurs in up to 7% of pregnant women and 30–40% will subsequently develop UTI or pyelonephritis if untreated. Persistent untreated bacteriuria places patient at a higher risk for preterm labor, low birth weight, and perinatal mortality. Escherichia coli are responsible for 70–90% of infections.

History/Pe

- **Asymptomatic bacteriuria:** ⊕ urine culture on first-trimester screen ($\geq 10^5$ colonies).
- **UTI:** Dysuria, urinary urgency and frequency.
- **Pyelonephritis:** Same as UTI, + fever and costovertebral angle tenderness.

Diagnosis

⊕ urine culture.

Treatment

- **Asymptomatic bacteriuria and UTI:** 3–7 days nitrofurantoin, cephalexin, or amoxicillin-clavulanate. Follow-up culture at 1 week as test of cure.
- **Pyelonephritis:** Admit to hospital, IV fluids, IV third-generation cephalosporins; Suppressive antibiotics with agent culture susceptible for remainder of pregnancy and follow-up culture.

ANTEPARTUM HEMORRHAGE

- Any bleeding that occurs after 20 weeks' gestation.
- Complicates 3–5% of pregnancies.
- The most common causes are **placental abruption** and **placenta previa** (see Table 2.11-14 and Figure 2.11-7).
- Other causes include other forms of abnormal placentation (eg, placenta accreta), ruptured uterus, genital tract lesions, and trauma.

KEY FACT

With third-trimester bleeding, think anatomically:

- **Vagina:** Bloody show, trauma.
- **Cervix:** Cervical cancer, cervical/vaginal lesion.
- **Placenta:** Placental abruption, placenta previa.
- **Fetus:** Fetal bleeding.

Obstetric Complications of Pregnancy

ECTOPIC PREGNANCY

Most often tubal, but can be abdominal, ovarian, or cervical.

History/Pe

- Presents with abdominal pain and vaginal spotting/bleeding, although some patients are asymptomatic.
- Associated with etiologies that cause scarring to the fallopian tubes, including a history of PID, pelvic surgery, DES use, or endometriosis.
- The differential Dx includes surgical abdomen, abortion, ovarian torsion, PID, and ruptured ovarian cyst.

A

The patient has severe preeclampsia. Start a magnesium sulfate drip for seizure prophylaxis and deliver by induction or C-section.

TABLE 2.11-14. Placental Abruption vs Placenta Previa vs Vasa Previa

Variable	placental abruption	placenta previa	Vasa previa
Pathophysiology	Premature (before delivery) separation of normally implanted placenta.	Abnormal placental implantation: ▪ **Total:** Placenta covers the cervical os. ▪ **Marginal:** Placenta extends to the margin of the os. ▪ **Low lying:** Placenta is in close proximity to the os.	Velamentous umbilical cord insertion and/or bilobed placenta causing vessels to pass over the internal os.
Incidence	1 in 100.	1 in 200.	1 in 2500.
Risk factors	Hypertension, abdominal/pelvic trauma, tobacco or cocaine use, previous abruption, rapid decompression of an overdistended uterus, excessive stimulation.	Prior C-sections, grand multiparity, advanced maternal age, multiple gestation, prior placenta previa.	Multiple gestation, IVF, accessory placental lobes, single umbilical artery, placenta previa, low-lying placenta.
Symptoms	**Painful, dark** vaginal bleeding that does not spontaneously cease. Abdominal pain; uterine hypertonicity. Fetal distress.	**Painless, bright red** bleeding that often ceases in 1–2 hours with or without uterine contractions. Usually no fetal distress.	**Painless bleeding at rupture of membranes with fetal bradycardia.**
Diagnosis	Primarily clinical. Transabdominal/transvaginal ultrasonography sensitivity is only 50%; look for a retroplacental clot. Most useful for ruling out previa.	Transabdominal/transvaginal ultrasonography sensitivity is > 95%; look for an abnormally positioned placenta.	Transvaginal ultrasonography with color Dopplers showing vessels passing over the internal os.
Management	Stabilize patients with mild abruption and a premature fetus; **manage expectantly** (hospitalize; start IV and fetal monitoring; type and cross-match blood; bed rest). **Moderate to severe abruption: Immediate delivery** is indicated (vaginal delivery with amniotomy if mother and fetus are stable and delivery is expected soon; C-section for maternal or fetal distress).	**Do not perform a vaginal exam!** Stabilize patients with a premature fetus; manage expectantly. Give tocolytics. Serial ultrasonograms to assess fetal growth; resolution of partial previa. Betamethasone 28–32 weeks to help with fetal lung maturity. **Deliver by C-section.** Indications for delivery include labor, life-threatening bleeding, fetal distress, documented fetal lung maturity, and 36 weeks GA.	**Acute bleeding = emergency C-section delivery.** **Diagnosis prior to bleeding: Steroids at 28–32 weeks to help with fetal lung maturity, hospitalization at 30–32 weeks for close monitoring and scheduled C-section delivery at 35 weeks.**
Complications	Hemorrhagic shock. DIC occurs in 10% of patients. Recurrence risk is 5–16% and ↑ to 25% after 2 previous abruptions. Fetal hypoxia.	↑ risk of placenta accreta. Vasa previa (fetal vessels crossing the internal os). Preterm delivery, PROM, IUGR, congenital anomalies. Recurrence risk is 4–8%.	Fetal exsanguination.

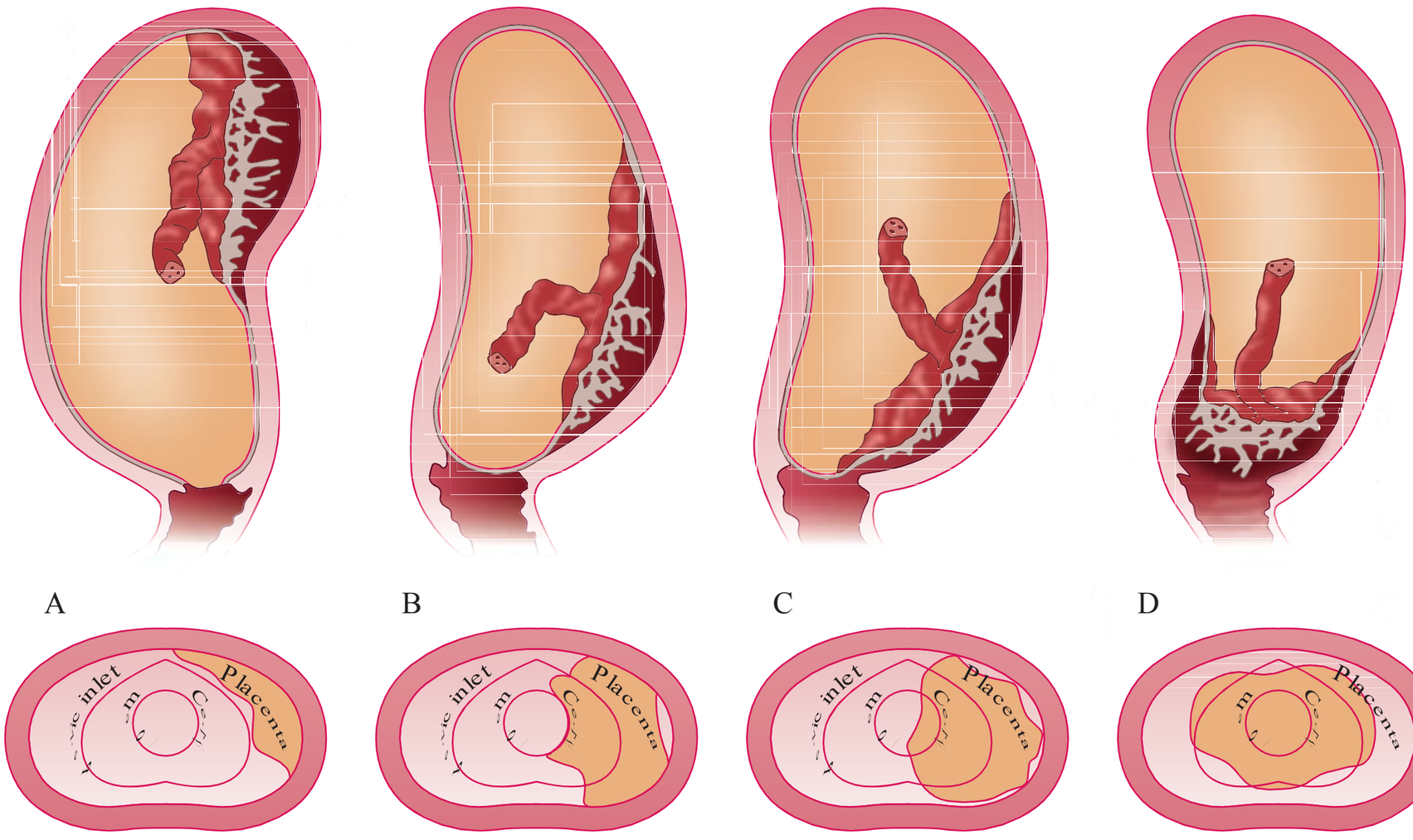


FIGURE 2.11-7. Placental implantation. (A) Normal placenta. **(B)** Low implantation. **(C)** Partial placenta previa. **(D)** Complete placenta previa. (Adapted with permission from DeCherney AH. Current Obstetric &Gynecologic Diagnosis &Treatment, 8th ed. Stamford, CT: Appleton &Lange; 1994.)

MNEMONIC

The classic triad of ectopic pregnancy **PAVE**s the way for diagnosis—

Pain (abdominal)
Amenorrhea
Vaginal bleeding
Ectopic pregnancy

Diagnosis

Approach a woman of reproductive age presenting with abdominal pain as a ruptured ectopic pregnancy until proven otherwise.

- Look for a ⊕ pregnancy test and a transvaginal ultrasonogram showing an empty uterus (see Figure 2.11-8).
- Confirm with a serial β-hCG without appropriate β-hCG doubling.

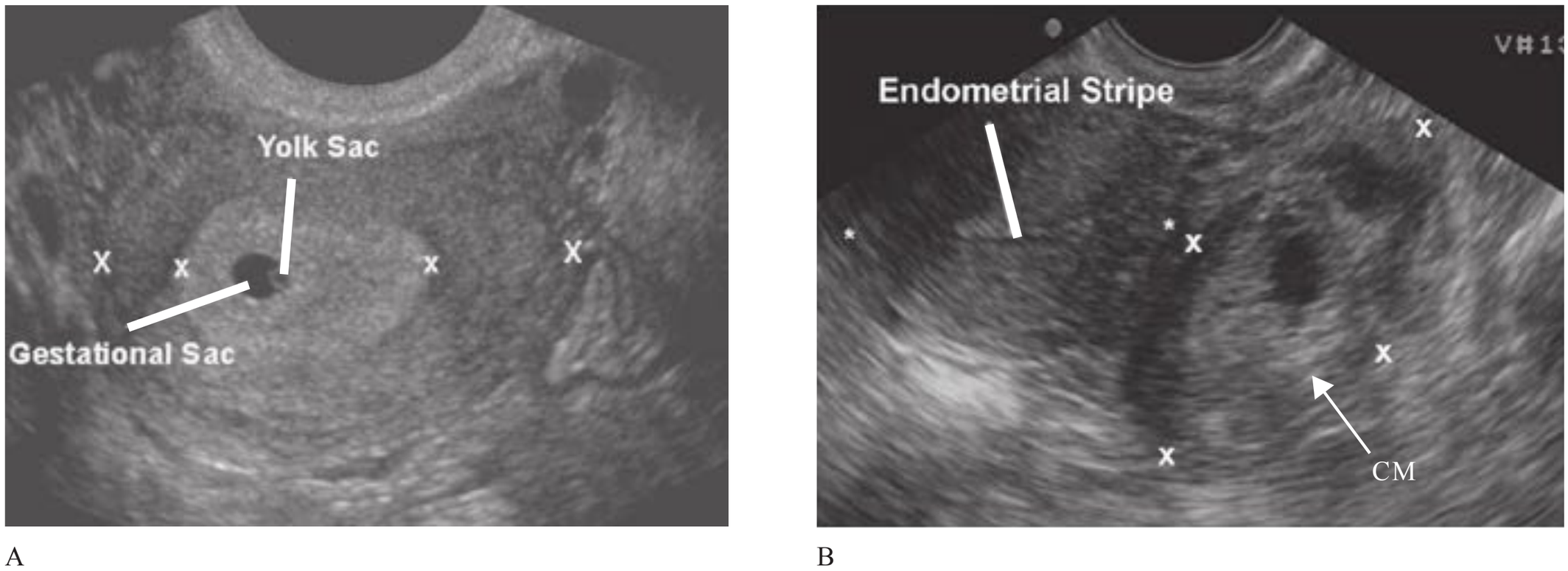


FIGURE 2.11-8. Normal intrauterine pregnancy and ectopic pregnancy. Transvaginal ultrasonogram showing **(A)** a normal intrauterine pregnancy with a gestational sac containing a yolk sac within the uterine cavity, and **(B)** a complex mass (CM)/ectopic pregnancy adjacent to an empty uterus. (Reproduced with permission from Tintinalli JE et al. Tintinalli's Emergency Medicine: A Comprehensive Study Guide, 6th ed. New York, NY: McGraw-Hill; 2004.)

Treatment

- Medical treatment (methotrexate) is sufficient for small, unruptured tubal pregnancies.
- Surgical options include salpingectomy or salpingostomy with evacuation (laparoscopy vs laparotomy).

Complications

Tubal rupture and hemoperitoneum (an obstetric emergency).

KEY FACT

Unstable patients or those with signs of peritoneal irritation (eg, rebound tenderness) require emergent surgical intervention.

INTRAUTERINE GROWTH RESTRICTION

An EFW less than the 10th percentile for GA.

History/Pe

Risk factors include the following:

- Maternal systemic disease leading to uteroplacental insufficiency (intrauterine infection, hypertension, anemia).
- Maternal substance abuse.
- Placenta previa.
- Multiple gestations.

Diagnosis

- Confirm serial fundal height measurements with ultrasonography.
- Perform ultrasonography for EFW.

Treatment

- Explore the underlying etiology, and correct if possible.
- **If the patient is near due date,** administer steroids (eg, betamethasone) to accelerate fetal lung maturity; requires 48 hours prior to delivery.
- Perform fetal monitoring with NST, CST, BPP, and umbilical artery Doppler velocimetry.
- A nonreassuring status near term may prompt delivery.

Complications

↑ perinatal morbidity and mortality.

FETAL MACROSOMIA

- Defined as a birth weight > 95th percentile. A common sequela of gestational diabetes.
- **Dx:** Weigh the newborn at birth (prenatal diagnosis is imprecise).
- **Tx:** Planned cesarean delivery may be considered for an EFW > 5000 g in women without diabetes and for an EFW > 4500 g in women with diabetes.
- **Complications:** ↑ risk of shoulder dystocia (leading to brachial plexus injury and Erb-Duchenne palsy) as birth weight ↑.

POLYHYDRAMNIOS

- An AFI ≥ 25 on ultrasonography. May be present in normal pregnancies, but fetal chromosomal developmental abnormalities must be considered. Etiologies include the following:
  - Maternal DM.
  - Multiple gestation.
  - Isoimmunization.
  - Pulmonary abnormalities (eg, cystic lung malformations).
  - Fetal anomalies (eg, duodenal atresia, tracheoesophageal fistula, anencephaly).
  - Twin-twin transfusion syndrome.
- **Hx/PE:** Usually asymptomatic.
- **Dx:** Fundal height greater than expected. Evaluation includes ultrasonography for fetal anomalies, glucose testing for DM, and Rh screen.
- **Tx:** Etiology specific.
- **Complications:** Preterm labor, fetal malpresentation, cord prolapse.

OLIGOHYDRAMNIOS

- An AFI < 5 on ultrasonography. Usually asymptomatic, but IUGR or fetal distress may be present.
- Etiologies include the following:
  - Fetal urinary tract abnormalities (eg, renal agenesis, GU obstruction).
  - Chronic uteroplacental insufficiency.
  - ROM.
- **Dx:** The sum of the deepest amniotic fluid pocket in all four abdominal quadrants on ultrasonography.
- **Tx:** Rule out inaccurate gestational dates. Treat the underlying cause if possible.
- **Complications:**
  - Associated with a 40-fold ↑ in perinatal mortality.
  - Other complications include musculoskeletal abnormalities (eg, clubfoot, facial distortion), pulmonary hypoplasia, umbilical cord compression, and IUGR.

RH ISOIMMUNIZATION

In this condition, fetal RBCs leak into the maternal circulation, and maternal anti-Rh IgG antibodies form that can cross the placenta, leading to hemolysis of fetal Rh RBCs (**erythroblastosis fetalis;** see Figure 2.11-9). Occurs only in

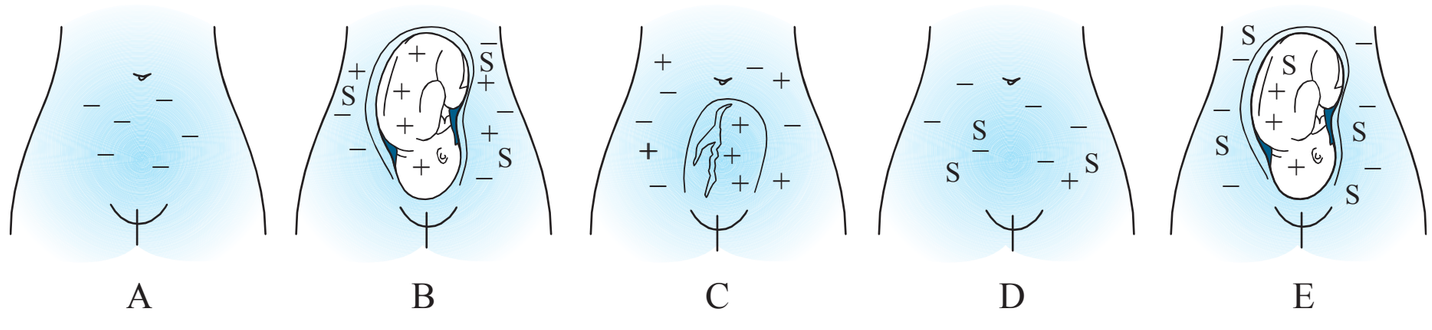


FIGURE 2.11-9. Rh isoimmunization. (A) Rh-⊖ mother prior to pregnancy. **(B)** Rh-⊕ fetus in Rh-⊖ mother. **(C)** Placental separation. **(D)** After delivery, the mother develops antibodies (S) to Rh antigen. **(E)** Rh-⊕ fetus in the next pregnancy. Maternal antibodies, from Rh isoimmunization at the time of the previous delivery, cross the placenta and cause hemolysis of RBCs in the fetus. (Reproduced with permission from DeCherney AH, Nathan L. Current Diagnosis & Treatment Obstetrics & Gynecology, 10th ed. New York, NY: McGraw-Hill; 2007.)

Rh-⊖ women; ↑ risk with previous SAB or TAB or previous delivery with no RhoGAM given.

Diagnosis

Sensitized Rh-⊖ mothers with titers > 1:16 should be closely monitored with serial ultrasonograms and amniocentesis for evidence of fetal hemolysis.

Treatment

In severe cases, initiate preterm delivery when fetal lungs are mature. Prior to delivery, intrauterine blood transfusions can be given to correct a low fetal hematocrit.

Prevention

- If the mother is Rh ⊖ at 28 weeks and the father is Rh ⊕ or unknown, give **RhoGAM** (Rh immune globulin).
- If the baby is Rh ⊕, give the mother RhoGAM postpartum.
- Give RhoGAM to Rh-⊖ mothers who undergo abortion or who have had an ectopic pregnancy, amniocentesis, vaginal bleeding, or placenta previa/placental abruption. **Type and screen is critical;** follow β-hCG closely and prevent pregnancy for 1 year.

Complications

- Hydrops fetalis when fetal hemoglobin is < 7 g/dL.
- Fetal hypoxia and acidosis, kernicterus, prematurity, death.

GESTATIONAL TROPHOBLASTIC DISEASE

A range of proliferative trophoblastic abnormalities that can be benign or malignant.

- **Benign GTD:** Includes complete and incomplete molar pregnancies (see Table 2.11-15).
- **Malignant GTD:** Molar pregnancy may progress to malignant GTD, including:
  - **Invasive moles:** 10–15%.
  - **Choriocarcinoma:** 2–5%.
- Complications of malignant GTD include pulmonary or CNS metastases and trophoblastic pulmonary emboli.

History/Pe

- Presents with first-trimester **uterine bleeding,** hyperemesis gravidarum, preeclampsia/eclampsia at < 24 weeks, and uterine size greater than dates.

TABLE 2.11-15. Complete vs Incomplete Moles

Variable	Complete	Incomplete
Mechanism	Sperm fertilization of an empty ovum.	Normal ovum fertilized by two sperm.
Karyotype	46,XX.	69,XXY.
Fetal tissue	No fetal tissue.	Contains fetal tissue.

- Risk factors include extremes of age (< 20 or > 40 years) and a diet deficient in folate or β-carotene.

Diagnosis

- No fetal heartbeat is detected.
- Pelvic examination may reveal enlarged ovaries (bilateral theca-lutein cysts) or expulsion of **grapelike molar clusters** into the vagina.
- Labs show markedly ↑ serum **β-hCG (usually > 100,000 mIU/mL).**
- Pelvic ultrasonography reveals a "snowstorm" appearance with no gestational sac or fetus present (see Figure 2.11-10).
- CXR may show lung metastases.
- D&C reveals **"cluster-of-grapes"** tissue.

Treatment

- Evacuate the uterus, and follow with weekly **β-hCG.**
- Treat malignant disease with chemotherapy (methotrexate or dactinomycin).
- Treat residual uterine disease with hysterectomy.
- Chemotherapy and irradiation are highly effective for metastases.

MULTIPLE GESTATIONS

- Affect 3% of all live births.
- Since 1980, the incidence of monozygotic (identical) twins has remained steady, whereas the incidence of dizygotic (fraternal) and higher order births has ↑.
- **Hx/PE:** Characterized by rapid uterine growth, excessive maternal weight gain, and palpation of three or more large fetal parts on Leopold maneuvers.
- **Dx:** Ultrasonography; β-hCG, human placental lactogen, and MSAFP are elevated for GA.
- **Tx:**
  - Multifetal reduction and selective fetal termination is an option for higher-order multiple pregnancies.
  - Antepartum fetal surveillance for IUGR.
  - Management by a high-risk specialist is recommended.

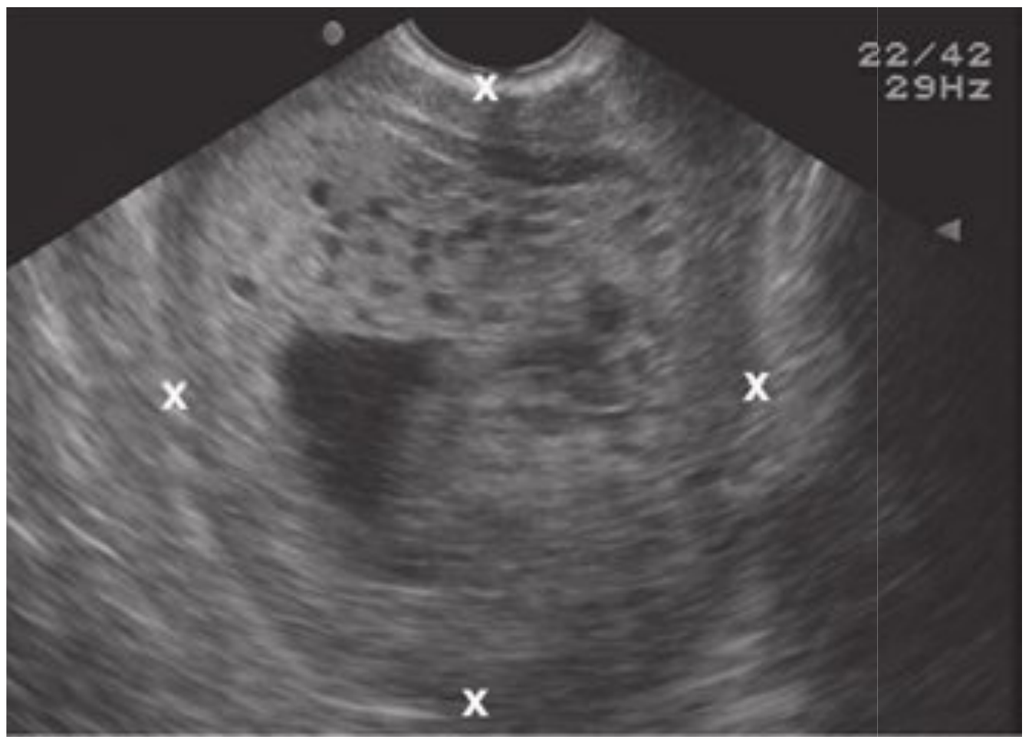


FIGURE 2.11-10. Molar pregnancy. Transvaginal ultrasonogram shows a large, complex intrauterine mass with cystic regions that have the characteristic appearance of grapes. (Reproduced with permission from Tintinalli JE et al. Tintinalli's Emergency Medicine: A Comprehensive Study Guide, 6th ed. New York, NY: McGraw-Hill; 2004.)

- **Complications:**
  - **Maternal:** Patients are six times more likely to be hospitalized with complications of pregnancy. There is a higher incidence of placenta previa and need for cesarian delivery.
  - **Fetal:** Twin-to-twin transfusion syndrome, IUGR, preterm labor, and a higher incidence of congenital malformations.

Abnormal Labor and Delivery

SHOULDER DYSTOCIA

Affects 0.6–1.4% of all deliveries in the United States. Risk factors include obesity, diabetes, a history of a macrosomic infant, and a history of prior shoulder dystocia.

Diagnosis

Diagnosed by a prolonged second stage of labor, recoil of the perineum ("turtle sign"), and lack of spontaneous restitution.

Treatment

In the event of dystocia, be the mother's **HELPER:**

- **H**elp reposition.
- **E**pisiotomy.
- **L**eg elevated (McRoberts maneuver; see Figure 2.11-11).
- **P**ressure (suprapubic).

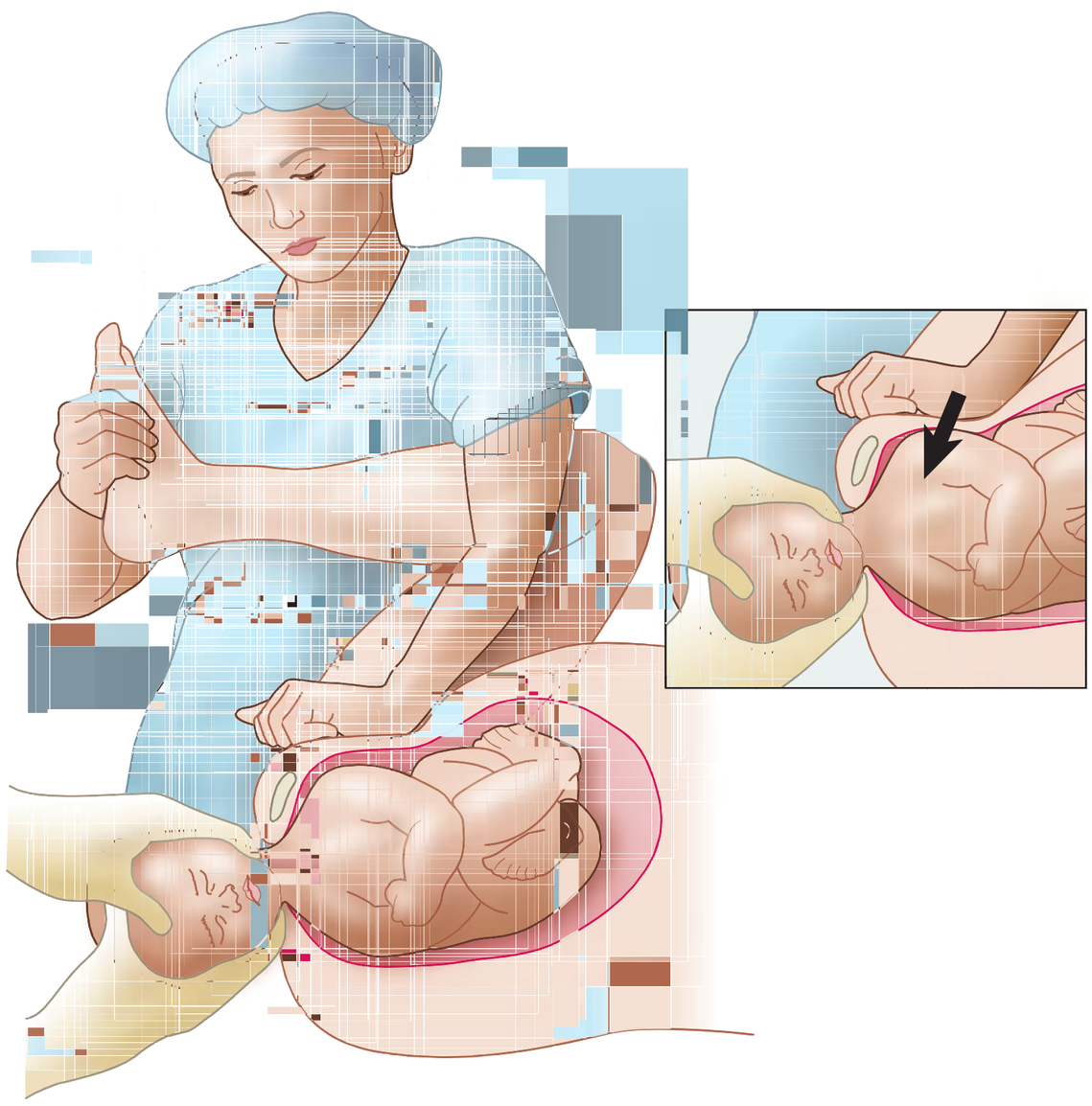


FIGURE 2.11-11. Leg elevation (McRoberts maneuver). The leg positioning illustrated here can be used to assist in a delivery where the infant is at risk for shoulder dystocia. (Reproduced with permission from Cunningham FG et al. Williams Obstetrics, 23rd ed. New York, NY: McGraw-Hill; 2010.)

- **E**nter the vagina and attempt rotation (Woods screw maneuver).
- **R**each for the fetal arm.

FAILURE TO PROGRESS

Associated with chorioamnionitis, occiput posterior position, nulliparity, and elevated birth weight.

Diagnosis

- **First-stage protraction or arrest:** Labor that fails to produce adequate rates of progressive cervical change.
- **Prolonged second-stage arrest:** Arrest of fetal descent. See Table 2.11-16 for definitions based on parity and anesthesia.

Treatment

See Table 2.11-16.

Complications

- Chorioamnionitis leads to fetal infection, pneumonia, and bacteremia.
- Permanent injury occurs in 10%.
- The risk of postpartum hemorrhage is 11%; that of fourth-degree laceration is 3.8%.

RUPTURE OF MEMBRANES

Distinguished as follows:

- **Spontaneous ROM:** Occurs after or at the onset of labor.
- **Premature ROM:** Occurs > 1 hour before onset of labor. May be precipitated by vaginal or cervical infections, abnormal membrane physiology, or cervical incompetence.

TABLE 2.11-16. Failure to Progress

Stage	Definition	Treatment[a]
First Stage: Failure to have progressive cervical change		
Latent	■ **Prima:** > 20 hours ■ **Multi:** > 14 hours	Therapeutic rest via parenteral analgesia; oxytocin; amniotomy; cervical ripening.
Active	■ **Prima:** > 2 hours ■ **Multi:** > 2 hours after reaching 3–4 cm	Amniotomy; oxytocin; C-section if the previous interventions are ineffective.
Second Stage: arrest of Fetal descent		
	■ **Prima:** > 2 hours; > 3 hours with epidural ■ **Multi:** > 1 hour; > 2 hours with epidural	Close observation with a ↓ in epidural rate and continued oxytocin. Assisted vaginal delivery (forceps or vacuum). C-section.

[a]Augmentation with oxytocin should be considered when contraction frequency is < 3 in a 10-minute period or intensity of contraction is < 25 mm Hg above baseline.

- **Preterm premature ROM (PPROM):** ROM occurring at < 37 weeks' gestation.
- **Prolonged ROM:** ROM occurring > 18 hours prior to delivery. Risk factors include low socioeconomic status (SES), young maternal age, smoking, and STDs.

History/Pe

Patients often report a **"gush" of clear or blood-tinged amniotic fluid.** Uterine contractions may be present.

Diagnosis

- A **sterile speculum exam** reveals pooling of amniotic fluid in the vaginal vault.
- **Nitrazine paper test** is ⊕ (paper turns blue, indicating alkaline pH of amniotic fluid).
- **Fern test** is ⊕ (a ferning pattern is seen under a microscope after amniotic fluid dries on a glass slide).
- Ultrasonography to assess amniotic fluid volume.
- **If the diagnosis is uncertain,** ultrasonography-guided transabdominal instillation of indigo carmine dye can be used to check for leakage (unequivocal test).
- Minimize infection risk; do not perform digital vaginal exams on women who are not in labor or for whom labor is not planned immediately.
- Check fetal heart tracing, maternal temperature, WBC count, and uterine tenderness for evidence of chorioamnionitis.

KEY FACT

To minimize the risk of infection, do not perform digital vaginal exams on women with PROM.

Treatment

- Depends on GA and fetal lung maturity.
  - **Term:** First check GBS status and fetal presentation; then labor may be induced or the patient can be observed for 6 hours.
  - > **34–36 weeks GA:** Labor induction may be considered.
  - < **32 weeks GA:** Expectant management with bed rest and pelvic rest.
- **Antibiotics:** To prevent infection and to prolong the latency period in the absence of infection.
- **Antenatal corticosteroids:**
  - Give betamethasone or dexamethasone × 48 hours.
  - Promotes fetal lung maturity in the absence of intra-amniotic infection prior to 32 weeks GA.
- If signs of infection or fetal distress develop, give antibiotics (ampicillin and gentamicin) and induce labor.

Complications

Preterm labor and delivery, chorioamnionitis, placental abruption, cord prolapse.

PRETERM LABOR

Onset of labor between **20 and 37 weeks' gestation.** The 1° cause of neonatal morbidity and mortality.

- Risk factors include multiple gestation, infection, PROM, uterine anomalies, previous preterm labor or delivery, polyhydramnios, placental abruption, poor maternal nutrition, and low SES.
- **Most patients have no identifiable risk factors.**

KEY FACT

Preterm labor = regular uterine contractions + concurrent cervical change at < 37 weeks'gestation.

History/Pe

Presents with menstrual-like cramps, onset of low back pain, pelvic pressure, and new vaginal discharge or bleeding.

Diagnosis

- Requires the following:
  - **Regular uterine contractions** (three or more contractions of 30 seconds each over a 30-minute period) and
  - **Concurrent cervical change** at < 37 weeks' gestation.
- Assess for contraindications to tocolysis such as infection, nonreassuring fetal testing, or placental abruption.
- **Sterile speculum exam** to rule out PROM.
- **Ultrasonography** to rule out fetal or uterine anomalies, verify GA, and assess fetal presentation and amniotic fluid volume.
- Obtain cultures for chlamydia, gonorrhea, and GBS; obtain a UA and urine culture.

Treatment

- Hydration and bed rest.
- **Tocolytic therapy** (β-mimetics, $MgSO_4$, CCBs, prostaglandin inhibitors) unless contraindicated.
- **Steroids** to accelerate fetal lung maturation.
- **Penicillin or ampicillin for GBS prophylaxis** if preterm delivery is likely.

Complications

RDS, intraventricular hemorrhage, **PDA,** necrotizing enterocolitis, retinopathy of prematurity, bronchopulmonary dysplasia, death.

FETAL MALPRESENTATION

Any presentation other than vertex (ie, head closest to birth canal, chin to chest, occiput anterior). Risk factors include **prematurity,** prior breech delivery, uterine anomalies, poly- or oligohydramnios, multiple gestations, PPROM, hydrocephalus, anencephaly, and placenta previa.

History/Pe

Breech presentations are the most common form and involve presentation of the fetal lower extremities or buttocks into the maternal pelvis (see Figure 2.11-12). Subtypes include the following:

- **Frank breech (50–75%):** The thighs are flexed and the knees are extended.
- **Footling breech (20%):** One or both legs are extended below the buttocks.
- **Complete breech (5–10%):** The thighs and knees are flexed.

KEY FACT

Breech presentation is the most common fetal malpresentation.

Treatment

- **Follow:** Up to 75% spontaneously change to vertex by week 38.
- **External version:** If the fetus has not reverted spontaneously, a version may be attempted by applying directed pressure to the maternal abdomen to turn the infant to vertex. The success rate is roughly 50%. Risks of version are placental abruption and cord compression, so be prepared for an emergency C-section if needed.
- **Trial of breech vaginal delivery:** Attempt only if delivery is imminent. Complications include cord prolapse and/or head entrapment.
- **Elective C-section:** Recommended given the lower risk of fetal morbidity.

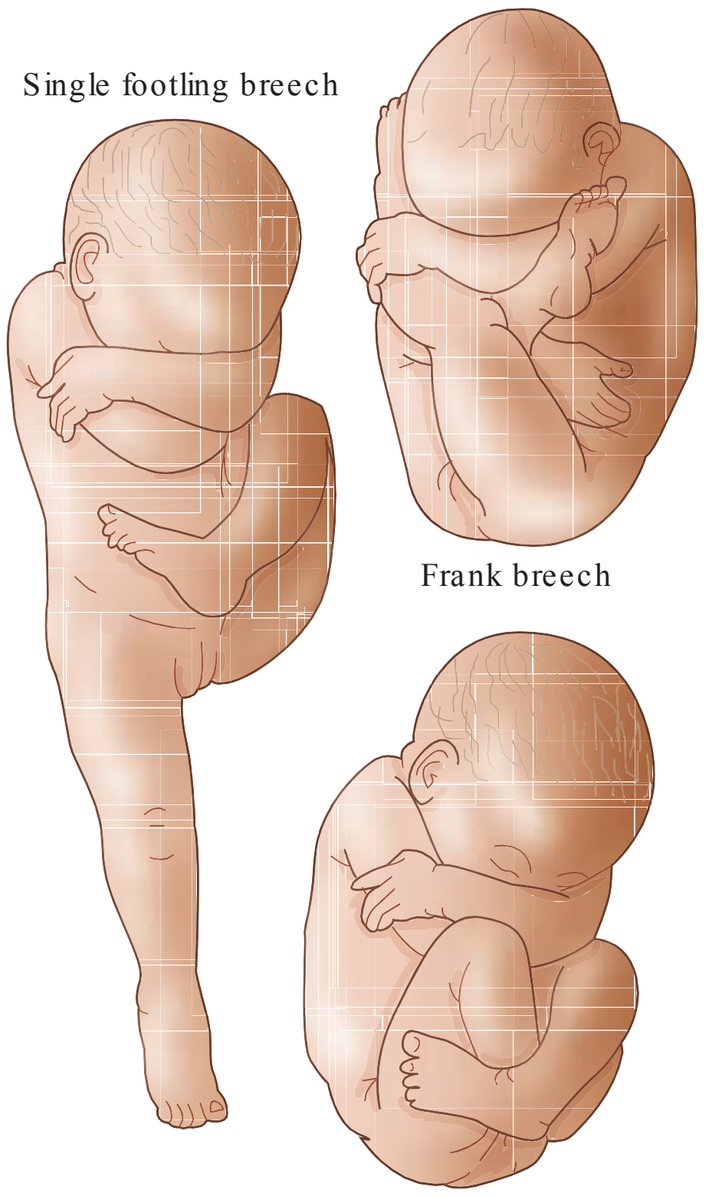


FIGURE 2.11-12. Types of breech presentations. (Reproduced with permission from DeCherney AH. Current Obstetric & Gynecologic Diagnosis & Treatment, 8th ed. Stamford, CT: Appleton & Lange; 1994.)

INDICATIONS FOR CESAREAN SECTION

See Table 2.11-17 for indications. For both elective and indicated cesarean delivery, sodium citrate should be used in the mother to ↓ gastric acidity and prevent acid aspiration syndrome.

EPISIOTOMY

- Surgical extension of the vaginal opening into the perineum.
- Can be **median** (midline) or **mediolateral.**

TABLE 2.11-17. Indications for Cesarean Section

Maternal Factors	Fetal and Maternal Factors	Fetal Factors
Prior classical C-section (vertical incision predisposes to uterine rupture with vaginal delivery).	Cephalopelvic disproportion (the most common cause of 1° C-section).	Fetal malposition (eg, posterior chin, transverse lie, shoulder presentation).
Active genital herpes infection.	Placenta previa/placental abruption.	Fetal distress.
Cervical carcinoma.	Failed operative vaginal delivery.	Cord compression/prolapse.
Maternal trauma/demise.	Postterm pregnancy (relative indication).	Erythroblastosis fetalis (Rh incompatibility).
HIV infection.		
Prior transverse C-section (relative indication).		

- Complications include the following:
  - **Extension to the anal sphincter (third degree) or rectum (fourth degree):** More common with midline episiotomy.
  - **Other:** Bleeding, infection, dyspareunia, rectovaginal fistula formation, or maternal death (rare).
  - **Routine use of episiotomy is not recommended.**

Puerperium

POSTPARTUM HEMORRHAGE

- A loss of > **500 mL of blood for vaginal delivery** or > **1000 mL for C-section.**
- May occur before, during, or after delivery of the placenta.
- Table 2.11-18 summarizes common causes.
- Complications include the following:
  - Acute blood loss (potentially fatal).
  - Anemia due to chronic blood loss (predisposes to puerperal infection).
  - Sheehan syndrome.
- Severe postpartum hemorrhage may be controlled with uterine artery embolization.

KEY FACT

Postpartum endometritis:
- Fever > 38°C within 36 hours.
- Uterine tenderness.
- Malodorous lochia.

TABLE 2.11-18. Common Causes of Postpartum Hemorrhage

Variable	uterine atony	genital tract trauma	retained placental tissue
Risk factors	Uterine overdistention (multiple gestation, macrosomia, polyhydramnios). Exhausted myometrium (rapid or prolonged labor, oxytocin stimulation). Uterine infection. Conditions interfering with contractions (anesthesia, myomas, $MgSO_4$).	Precipitous labor. Operative vaginal delivery (forceps, vacuum extraction). Large infant. Inadequate episiotomy repair.	Placenta accreta/increta/percreta. Placenta previa. Uterine leiomyomas. Preterm delivery. Previous C-section/curettage.
Diagnosis	Palpation of a soft, enlarged, "boggy" uterus. The most common cause of postpartum hemorrhage (90%).	Manual and visual inspection of the lower genital tract for any laceration > 2 cm long.	Manual and visual inspection of the placenta and uterine cavity for missing cotyledons. Ultrasound may also be used to inspect the uterus.
Treatment[a]	Bimanual uterine massage (usually successful). Oxytocin infusion. Methergine (methylergonovine) if not hypertensive. PGF_{2a}.	Surgical repair of the physical defect.	Manual removal of remaining placental tissue. Curettage with suctioning (carries risk of uterine perforation).

[a]For all uterine causes, when bleeding persists after conventional therapy, uterine/internal iliac artery ligation, uterine artery embolization, or hysterectomy can be lifesaving.

POSTPARTUM INFECTIONS

- **A temperature ≥ 38°C for at least 2 of the first 10 postpartum days (not including the first 24 hours).**
- Risk factors for postpartum endometritis include emergent C-section, PROM, prolonged labor, multiple intrapartum vaginal exams, intrauterine manipulations, delivery, low SES, young age, prolonged ruptured membranes, bacterial colonization, and corticosteroid use.
- **Tx:** Broad-spectrum empiric IV antibiotics (eg, clindamycin and gentamicin) until patients have been afebrile for 48 hours (24 hours for chorioamnionitis). Add ampicillin for complicated cases.
- **Complications: Septic pelvic thrombophlebitis.**
  - Pelvic infection leads to infection of the vein wall and intimal damage, leading in turn to thrombogenesis. The clot is then invaded by microorganisms.
  - Suppuration follows, with liquefaction, **fragmentation, and, finally, septic embolization.**
  - Presents with abdominal and back pain and a "picket-fence" fever curve ("hectic" fevers) with wide swings from normal to as high as 41°C (105.8°F).
  - Diagnose with blood cultures and CT looking for a pelvic abscess.
  - Treat with broad-spectrum antibiotics and **anticoagulation** with heparin × 7–10 days.

MNEMONIC

The 7 W's of postpartum fever (10 days postdelivery)—
Womb (endomyometritis)
Wind (atelectasis, pneumonia)
Water (UTI)
Walk (DVT, pulmonary embolism)
Wound (incision, episiotomy)
Weaning (breast engorgement, abscess, mastitis)
Wonder drugs (drug fever)

SHEEHAN SYNDROME (POSTPARTUM PITUITARY NECROSIS)

- Pituitary ischemia and necrosis that lead to anterior pituitary insufficiency 2° to massive obstetric hemorrhage and shock.
- **Hx/PE:**
  - The 1° cause of anterior pituitary insufficiency in adult females.
  - **The most common presenting syndrome is failure to lactate (due to ↓ prolactin levels).**
  - Other symptoms include weakness, lethargy, cold insensitivity, genital atrophy, and menstrual disorders.
- **Dx:** Provocative hormonal testing and MRI of the pituitary and hypothalamus to rule out tumor or other pathology.
- **Tx:** Replacement of all deficient hormones. Some patients may recover TSH and even gonadotropin function after cortisol replacement alone.

LACTATION AND BREASTFEEDING

- During pregnancy, ↑ estrogen and progesterone result in breast hypertrophy and inhibition of the action of prolactin on the breast.
- After delivery of the placenta, hormone levels ↓ markedly, and prolactin stimulates the alveolar epithelial cells, activating milk production.
- Periodic infant suckling leads to further release of prolactin and oxytocin, which stimulate myoepithelial cell contraction and milk ejection ("let-down reflex").
- Colostrum ("early breast milk") contains protein, fat, **secretory IgA,** and minerals.
- Within 1 week postpartum, mature milk with protein, fat, lactose, and water is produced.
- High IgA levels in colostrum provide passive immunity for the infant and protect against enteric bacteria.

- Other potential benefits include the following:
  - ↓ incidence of infant allergies.
  - ↓ incidence of early URIs and GI infections.
  - Facilitation of mother-child bonding.
  - Maternal weight loss.
- Contraindications to breastfeeding include HIV infection, active HBV and HCV infection, and use of certain medications (eg, tetracycline, chloramphenicol).

MASTITIS

Cellulitis of the periglandular tissue caused by nipple trauma from breastfeeding coupled with the introduction of bacteria, usually Staphylococcus aureus, from the infant's pharynx into the nipple ducts.

History/Pe

- Symptoms often begin 2–4 weeks postpartum.
- Symptoms are **usually unilateral** and include the following:
  - Breast tenderness.
  - A palpable mass.
  - Erythema, edema, warmth, and possible purulent nipple drainage.
- Significant fever, chills, and malaise can also be seen.

Diagnosis

- Differentiate from simple breast swelling.
- Infection is suggested by focal symptoms, an ↑ WBC count, and fever.

Treatment

KEY FACT

The treatment of mastitis includes antibiotics and continued breastfeeding.

- **Continued breastfeeding** to prevent the accumulation of infected material (or use of a breast pump in patients who are no longer breastfeeding).
- **PO antibiotics** (dicloxacillin, cephalexin, amoxicillin/clavulanate, azithromycin, clindamycin).
- If not clinical improvement within 48–72 hours, evaluate with breast ultrasonography to assess for abscess. If present, treat with incision and drainage.

HIGH-YIELD FACTS IN

GYNECOLOGY

Menarche and Normal Female Development 332

Normal Menstrual Cycle 332

Menopause 333

Contraception 334

Abnormalities of the Menstrual Cycle 334

- 1° Amenorrhea/delayed Puberty 334
- 2° Amenorrhea 338
- 1° dysmenorrhea 340
- 2° dysmenorrhea 340
- Abnormal Uterine Bleeding 341

Reproductive Endocrinology 343

- congenital Adrenal Hyperplasia 343
- Polycystic ovarian Syndrome 345
- Infertility 346

Gynecologic Infections 347

- cyst and Abscess of Bartholin duct 347
- Vaginitis 348
- cervicitis 349
- Pelvic Inflammatory disease 349
- Toxic Shock Syndrome 350

Gynecologic Neoplasms 351

- Uterine Leiomyoma (Fibroids) 351
- Endometrial cancer 352
- cervical cancer 353
- Vulvar cancer 356
- Vaginal cancer 357
- ovarian cancer 357

Pelvic Organ Prolapse 359

Urinary Incontinence 360

Pediatric Gynecology 360

- Pediatric Vaginal discharge 360
- Precocious Puberty 361

Benign Breast Disorders 363

- Nonproliferative Breast Lesions 363
- Proliferative Breast Lesions Without Atypia 363
- Fibroadenoma 364
- Phyllodes Tumor 365
- Atypical Hyperplasia 365

Breast Cancer 365

Sexual Assault 368

Menarche and Normal Female Development

KEY FACT

Normal male development is later in onset with a different order: testicular enlargement (onset 9–14 years) → penile growth → pubarche → facial hair

- In order: Growth acceleration → thelarche (breast development, onset 8–11 years) → pubarche (pubic hair growth) → menarche (onset 10–16 years).
- Figure 2.12-1 graphically illustrates the stages of normal female development.

Normal Menstrual Cycle

The progression of a normal menstrual cycle is as follows (see also Figure 2.12-2):

Menstruation/follicular phase (days 1–13):

- Starts with menstruation and ends at LH surge/ovulation.
- May vary, but typically lasts ~ 13 days.
- ↑ frequency of GnRH pulse → ↑ FSH → growth of follicles → ↑ estrogen production.
- Results in the development of straight glands and thin secretions of the uterine lining (proliferative phase).
- By late follicular phase: Dominant follicle is selected and increases in size, uterine endometrium thickens, and cervical mucus becomes stringy.

KEY FACT

"LH surge" triggers ovulation and initiates production of progesterone.

Ovulation (day 14):

- Estradiol reaches a peak → positive feedback to the pituitary gland → LH surge (smaller FSH rise) → rupture of the ovarian follicle and release of a mature ovum → travels to oviduct/uterus.
- Ruptured follicular cells differentiate into the corpus luteum.

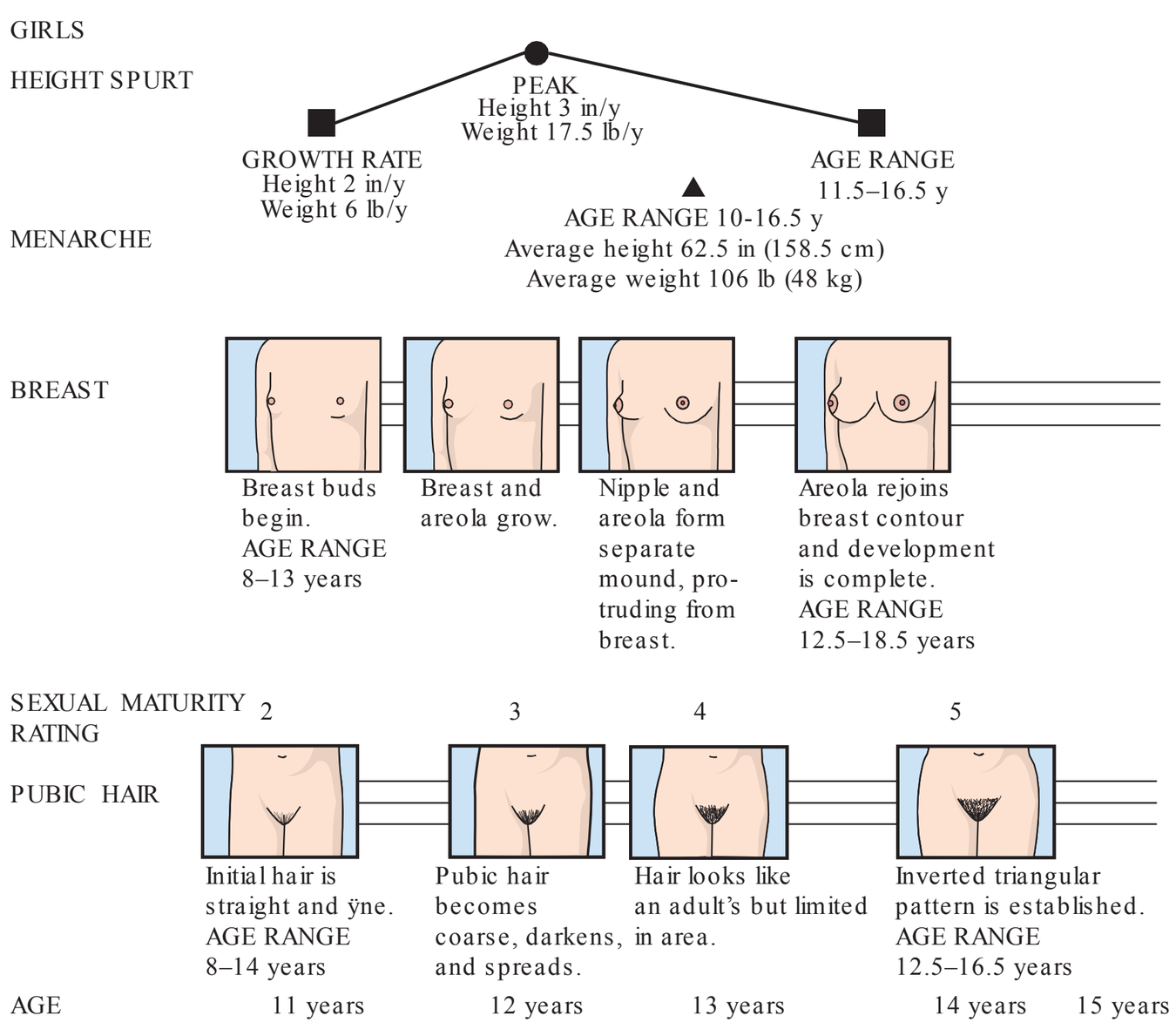


FIGURE 2.12-1. Normal female development. (Reproduced with permission from Hay WW Jr et al. Current Diagnosis & Treatment: Pediatrics, 19th ed. New York, NY: McGraw-Hill; 2008.)

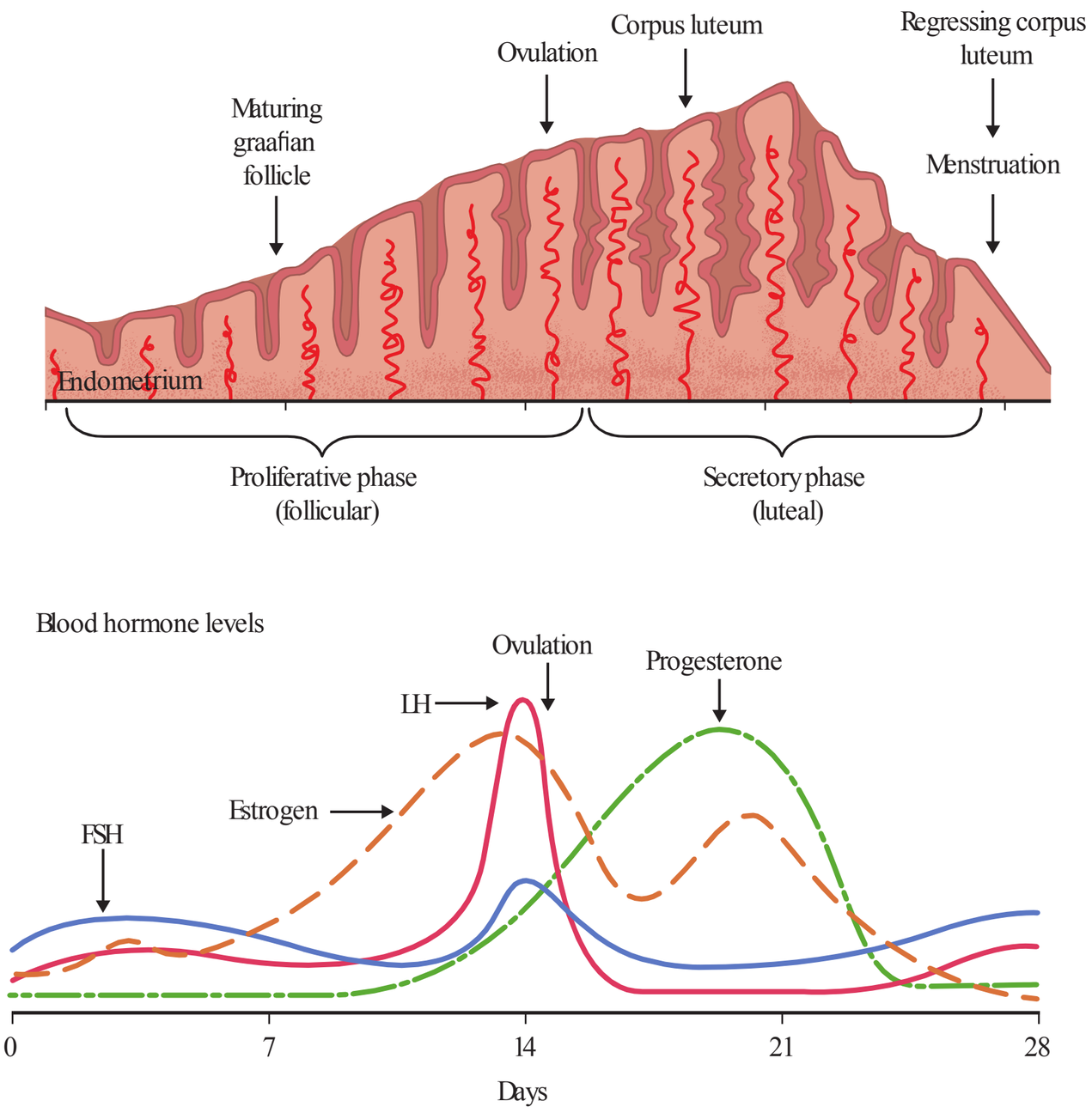


FIGURE 2.12-2. Normal menstrual cycle. (Adapted with permission from USMLE-Rx.com as published in Le T et al. First Aid for the USMLE Step 1 2015. New York, NY: McGraw-Hill; 2015.)

Luteal phase (days 15–28):

- The length of time (10–14 days) that the corpus luteum can survive without further LH or hCG stimulation.
- Change from estrogen to progesterone predominance: Corpus luteum produces progesterone and some estradiol, allowing the endometrial lining to develop thick and tortuous endometrial glands with thick secretions (secretory phase).
- In the absence of fertilization and implantation, ↓ LH → ↓ progesterone and estradiol by the corpus luteum → results in sloughing of the endometrial lining.
- With ↓ estrogen and progesterone there is no longer negative feedback to FSH, which then increases and restarts menstruation/follicular phase.

Menopause

Cessation of menses for a minimum of 12 months as a result of follicular depletion.

History/Pe

- The average age of onset is 51 years.
- Symptoms include hot flashes, vaginal atrophy (pruritus, vaginal dryness), insomnia, anxiety/irritability, poor concentration, mood changes, dyspareunia, and loss of libido.
- "Premature menopause" is cessation of menses before age 40.

Diagnosis

A clinical diagnosis. The following studies are not routine but may be helpful:

- **Labs: ↑ FSH;** then ↑ **LH.**
- **Lipid profile:** ↑ total cholesterol, ↓ HDL.

Treatment

- **Hormone replacement therapy (HRT; combination estrogen and progestin):**
  - If moderate to severe **vasomotor symptoms** → **SHORT**-term therapy.
  - May ↑ the incidence of breast cancer.
  - May ↑ cardiovascular morbidity and mortality.
  - **Contraindications:** Vaginal bleeding, breast cancer (known or suspected), untreated endometrial cancer, a history of thromboembolism, chronic liver disease, and hypertriglyceridemia.
- **Non-HRT:** SSRI/SNRIs, clonidine, and/or gabapentin to ↓ the frequency of hot flashes.
- **Topical estrogen preparation:** For **vaginal atrophy.** Does NOT have the same contraindications as systemic HRT.
- **Supplements ± bisphosphonates:** For **osteoporosis.** DEXA scan is used to measure bone mineral density (BMD). Supplemental treatment includes daily calcium/vitamin D and weight-bearing exercise.

KEY FACT

Postmenopausal women, should be routinely screened for osteoporosis starting at age 65, earlier if additional risk factors.

Contraception

Eighty-five percent of sexually active women with no contraception will become pregnant within 1 year.

- Table 2.12-1 describes the effectiveness of contraceptive methods along with their relative advantages and disadvantages.
- See Table 2.12-2 for contraindications to common methods of contraception.
- Emergency contraception (EC) methods prevent pregnancy after unprotected sex or contraceptive failure. Table 2.12-3 describes the various methods of EC.

KEY FACT

Multiple sexual partners and nulliparity are **not** absolute contraindications to IUD use.

KEY FACT

Combined hormonal methods of contraception protect against endometrial and ovarian cancer.

Abnormalities of the Menstrual Cycle

1° AMENORRHEA/DELAYED PUBERTY

The absence of menses by age 16 with 2° sexual development present, or the absence of 2° sexual characteristics by age 14.

History/Pe

- **Absence of 2° sexual characteristics** (no estrogen production).
  - **1° ovarian insufficiency:** Most common cause (~ 50%). Depletion of ovarian follicles and oocytes most commonly from Turner syndrome (45,XO). Also consider history of radiation therapy and chemotherapy.
  - **Central hypogonadism:** Can be caused by a variety of factors, including the following:
    - Undernourishment, stress, hyperprolactinemia, or exercise.
    - CNS tumor (consider prolactin-secreting pituitary adenoma if galactorrhea) or cranial irradiation.

KEY FACT

For Turner syndrome think streak gonads, shield chest, amenorrhea, webbed neck, aortic coarctation, and bicuspid aortic valve.

TABLE 2.12-1. Contraceptive Methods

Method	Mechanism	Advantages	Disadvantages
Most effective: > 99%			
Implanon (progestin-only implant)	Inhibits ovulation; ↑ cervical mucus viscosity.	Effective for up to 3 years. Immediate fertility once removed. Safe with breastfeeding. Lighter periods.	**Irregular periods,** scarring at site of insertion (typically arm), possible weight gain.
IUD with progestin (Mirena)	Foreign body results in inflammation; progesterone leads to cervical mucus thickening and endometrial decidualization.	Effective for up to 5 years. Immediate fertility once removed. Safe with breastfeeding. Lighter periods; less cramping.	Spotting (up to 6 months), acne. Risk of uterine perforation (1/1000). In rare pregnancy, ↑ risk of ectopic.
Copper T IUD (ParaGard)	Foreign body results in inflammation; copper has a spermicidal effect. No hormonal exposure.	Effective for up to 10 years. Immediate fertility once removed. Safe with breastfeeding.	↑ cramping and bleeding (5–10%). Risk of uterine perforation (1/1000). In rare pregnancy, ↑ risk of ectopic.
Surgical sterilization (vasectomy, tubal ligation)		Permanently effective; safe with breastfeeding.	**Tubal ligation:** Irreversible; in rare pregnancy: ↑ risk of ectopic. **Vasectomy:** Most failures are due to not waiting for 2 ⊖ semen samples.
Very effective: 90–99%			
Depo-Provera (medroxyprogesterone)	IM injection (progestin).	Lighter or no periods. Each shot works for 3 months. Safe with breastfeeding.	Irregular bleeding, **weight gain.** Decreases in BMD (reversible). Delayed fertility after discontinuation (up to 10 months).
Ortho Evra ("the patch")	Combined weekly estrogen and progestin dermal patch.	Periods may be more regular. Weekly administration.	Thromboembolism risk (especially in smokers > 35 years of age).
NuvaRing ("the ring")	Combined low-dose progestin and estrogen vaginal ring.	Can make periods more regular. 3 weeks—continuous; 1 week—no ring. Safe to use continuously.	May ↑ vaginal discharge. Spotting (first 1–2 months).
OCPs (combination estrogen and progestin)	Inhibit FSH/LH, suppressing ovulation; thicken cervical mucus; decidualize endometrium.	↓ risk of ovarian and endometrial cancers.[a] Predictable, lighter, less painful menses. Can improve acne. Immediate fertility upon cessation.	Requires daily compliance. Breakthrough bleeding (10–30%). Thromboembolism risk (especially in smokers > 35 years of age).
Progestin-only "minipills"	Thicken cervical mucus.	Safe with breastfeeding.	Requires strict compliance with daily timing.

(continues)

TABLE 2.12-1. Contraceptive Methods (continued)

Method	Mechanism	Advantages	Disadvantages
Moderately effective: 75–90%			
Male condoms	A latex sheath covers the penis.	The only method that effectively protects against pregnancy and STDs, including HIV.	Possible allergy to latex or spermicides.
Diaphragm with spermicide	A barrier is inserted over the cervix to prevent entry of sperm.	Some protection against STDs.	Must be fitted by the provider.
Female condom	A barrier sheath is inserted into the vagina.	Some protection against STDs.	Can be difficult to use.
Fertility awareness methods	Sexual intercourse is avoided on days in the menstrual cycle on which conception is likely (near the time of ovulation).	No side effects.	Requires the partner's participation. No STD/HIV protection.
Less effective: 68–74%			
Withdrawal	The penis is removed prior to ejaculation.	No side effects.	No STD/HIV protection. Not recommended as a 1° method.
Spermicide	A substance that inhibits sperm motility.	May be used as a 2° method.	Not recommended as a 1° method.

[a] Other combined hormonal methods (eg, patch, ring) may also protect against endometrial and ovarian cancer; however, data are still lacking given their relatively recent introduction.

TABLE 2.12-2. Contraindications to Common Methods of Contraception

Estrogen-Containing Hormonal Methods[a]	IUDs (Progesterone and Copper)
Pregnancy	Severe uterine structural abnormality (bicornuate, septate)
History of stroke, HTN, DVT/PE	Known or suspected pregnancy
Breast cancer	Active gynecologic infection (within 3 months)
Undiagnosed abnormal vaginal bleeding	Unexplained vaginal/uterine bleeding
Estrogen-dependent cancer	Suspected gynecologic malignancy
Benign or malignant liver neoplasm	**Copper T alone:**
Abnormal liver function	■ Copper intolerance (allergy, Wilson disease)
Current tobacco use **and** age > 35	■ Severe dysmenorrhea and/or menorrhagia
	Progestin IUD alone:
	■ Levonorgestrel allergy
	■ Breast cancer
	■ Acute liver disease or liver tumor

[a] Includes OCPs, NuvaRing, and Ortho Evra.

TABLE 2.12-3. Emergency Contraceptive Methods

Method	Advantages	Disadvantages
"Morning-after pill"[a] Combined estrogen/progestin (75% effective)	Available over the counter. Does not disrupt embryo postimplantation. Can be used as bridge contraception. Safe for all women.	Nausea, vomiting, fatigue, headache, dizziness, breast tenderness. No protection against STDs.
Progestin only (80% effective)	Same as above. Fewer nausea/vomiting side effects than combined EC.	Same as above.
Copper TIUD (99% effective)[b]	Can be used as EC and continued for up to 10 years of contraception.	High initial cost of insertion. Must be inserted by the provider. No protection against STDs. Must test for pregnancy and STDs prior to insertion.

[a] Used within 120 hours of unprotected sex.

[b] Used within 7 days of unprotected sex.

- Kallmann syndrome (isolated gonadotropin deficiency) associated with **anosmia.**
- **Constitutional growth delay.**

- **Presence of 2° sexual characteristics** (estrogen production but other anatomic or genetic problems): Etiologies include the following:
  - **Müllerian agenesis:** Absence of two-thirds of the vagina; uterine abnormalities.
  - **Imperforate hymen:** Presents with hematocolpos (blood in the vagina) that cannot escape, along with a bulging hymen.
  - **Complete androgen insensitivity:** Patients present with breast development (aromatization of testosterone to estrogen) but are amenorrheic and lack pubic hair.
  - **Congenital adrenal hyperplasia:** Can present as virilization with amenorrhea or oligomenorrhea.

KEY FACT

The first step in the workup of 1° or 2° amenorrhea is a pregnancy test!

Diagnosis

- **Get a pregnancy test.**
- Physical exam: Pubertal development, genital exam, signs of androgen excess, physical features of Turner syndrome.
- Assess for anatomic abnormalities (imperforate hymen): Physical exam, ultrasonography.
- Uterus absent: Karyotype and serum testosterone to assess if abnormal müllerian development (46,XX, normal female testosterone levels), and androgen insensitivity (46,XY, normal male testosterone levels).
- Uterus present: **FSH,** LH levels.
  - ↑ **FSH:** Primary ovarian insufficiency. Obtain karyotype for Turner syndrome (45,X).
  - **Normal/low FSH:** Central hypogonadism, constitutional growth delay. Measure serum prolactin, thyrotropin especially if galactorrhea.
- **If signs of hyperandrogenism:** Consider androgen-secreting neoplasm. Check serum testosterone, DHEAS.
- **If hypertensive:** Evaluate for congenital adrenal hyperplasia (CAH; 17-hydroxylase and 11-hydroxylase deficiencies).

See Table 2.12-4 for etiologies and Figure 2.12-3 for workup of 1° amenorrhea.

Treatment

- **Constitutional growth delay:** No treatment is necessary.
- **Hypogonadism:** Begin HRT with estrogen alone at the lowest dose. Begin cyclic estrogen/progesterone therapy 12–18 months later (if the uterus is present).
- **Anatomic:** Generally requires surgical intervention.

2° AMENORRHEA

The absence of menses for 6 consecutive months in women who have passed menarche. Etiology includes:

- **Pregnancy.**
- **Ovary:** PCOS, premature ovarian failure.
- **Hypothalamus:** Neoplasm, functional hypothalamic amenorrhea (nutrition, exercise, and stress), systemic illness (diabetes mellitus type 1 [DM1], celiac disease).
- **Pituitary:** Adenoma (eg, prolactin secreting), sellar masses, Sheehan syndrome.
- **Thyroid:** Hypothyroidism.
- **Uterine:** Asherman syndrome, cervical stenosis.

Diagnosis

- History and physical exam.
- Get a pregnancy test.
- If ⊖, measure TSH and prolactin.
- ↑ **TSH:** Indicates hypothyroidism.
- ↑ **prolactin** (inhibits the release of GnRH and thus LH and FSH): Points to a pituitary pathology. Order an MRI of the pituitary to look for a prolactin-secreting pituitary adenoma.

TABLE 2.12-4. Etiologies of 1° Amenorrhea

	GnRH	LH/FSH	Progesterone	Etiology
Constitutional growth delay	↓	↓	↓ (prepuberty levels)	Puberty has not started.
Hypogonadotropic hypogonadism	↓	↓ or normal	↓	Hypothalamic or pituitary problem.
Hypergonadotropic hypogonadism	↑	↑	↓	Ovaries have failed to produce estrogen.
Anovulatory problem	↑ or ↓	Normal	↑ estrogen/ ↓ progesterone	PCOS or a problem with estrogen receptors.
Anatomic problem	Normal	Normal	Normal	Menstrual blood cannot get out.

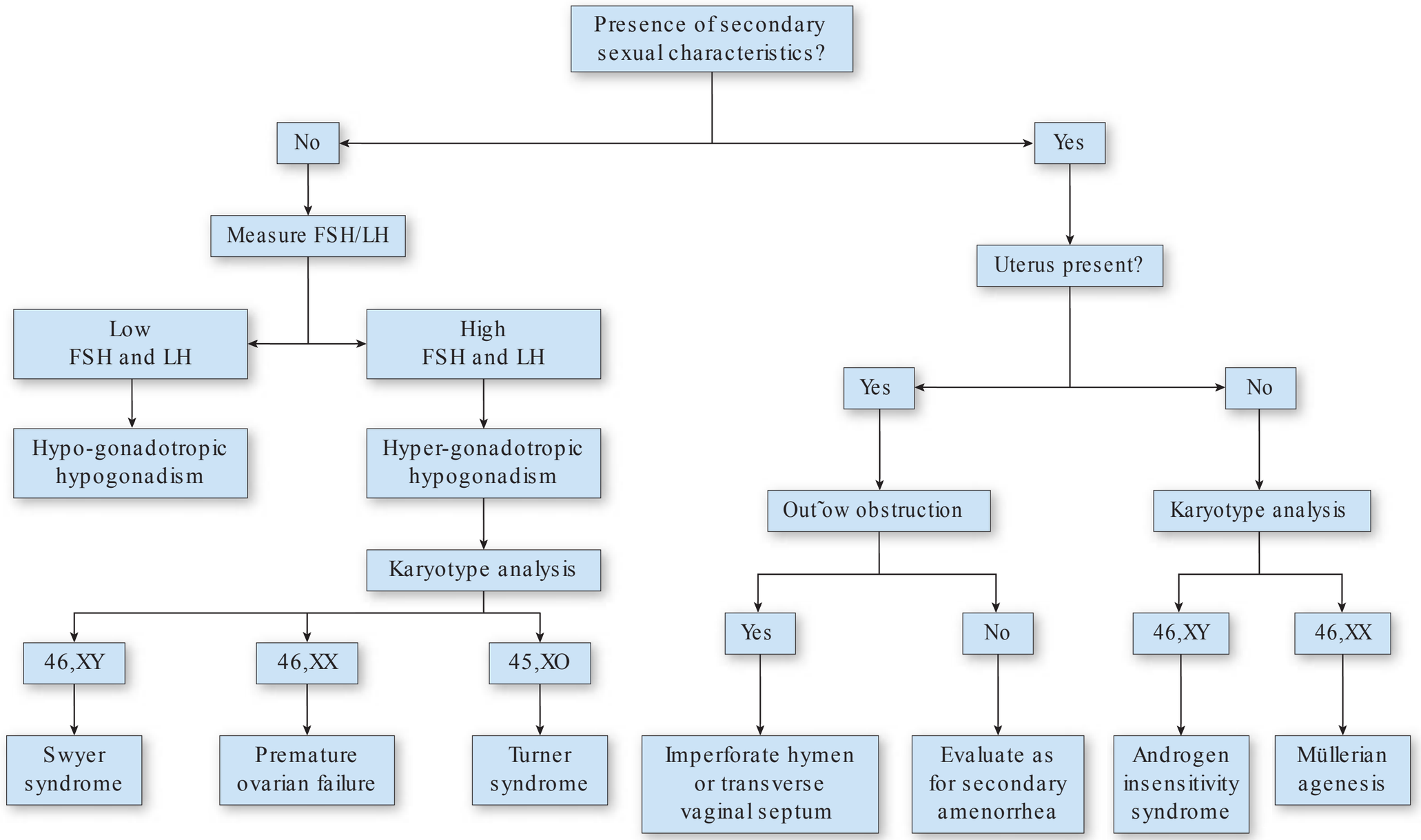


FIGURE 2.12-3. Workup of 1° amenorrhea. (Modified with permission from DeCherney AH et al. Current Diagnosis & Treatment: Obstetrics & Gynecology, 11th ed. New York, NY: McGraw-Hill; 2013.)

- **Initiate a progestin challenge** (10 days of progestin).
- See Figure 2.12-4 for an algorithm of the diagnostic workup.
- ⊕ **progestin challenge (withdrawal bleed):** Indicates anovulation that is probably due to noncyclic gonadotropin secretion, pointing to PCOS or idiopathic anovulation.
- ⊖ **progestin challenge (no bleed):** Indicates uterine abnormality or estrogen deficiency.
- **Signs of hyperglycemia (polydipsia, polyuria) or hypotension:** Conduct a 1-mg overnight dexamethasone suppression test to distinguish CAH (21-hydroxylase deficiency), Cushing syndrome, and Addison disease.
- **If clinical virilization is present:** Measure testosterone, DHEAS, and 17-hydroxyprogesterone.
- **Mild pattern:** PCOS, CAH, or Cushing syndrome.
- **Moderate to severe pattern:** Look for an ovarian or adrenal tumor.

Treatment

- **Hypothalamic:** Reverse the underlying cause, and induce ovulation with gonadotropins if trying to conceive. If not, oral contraceptives.
- **Tumors:** Excision; medical therapy for prolactinomas (eg, cabergoline, bromocriptine).
- **Premature ovarian failure (age < 40 years):** If the uterus is present, treat with combined oral contraceptives or estrogen plus progestin replacement therapy.

Q 1

A 56-year-old woman presents with complaints of insomnia, vaginal dryness, and lack of menses for 13 months. What is the most likely diagnosis?

Q 2

A 16-year-old girl presents with ↓ appetite, insomnia, and amenorrhea for 3 months. What is the most likely diagnosis, and how will you confirm it?

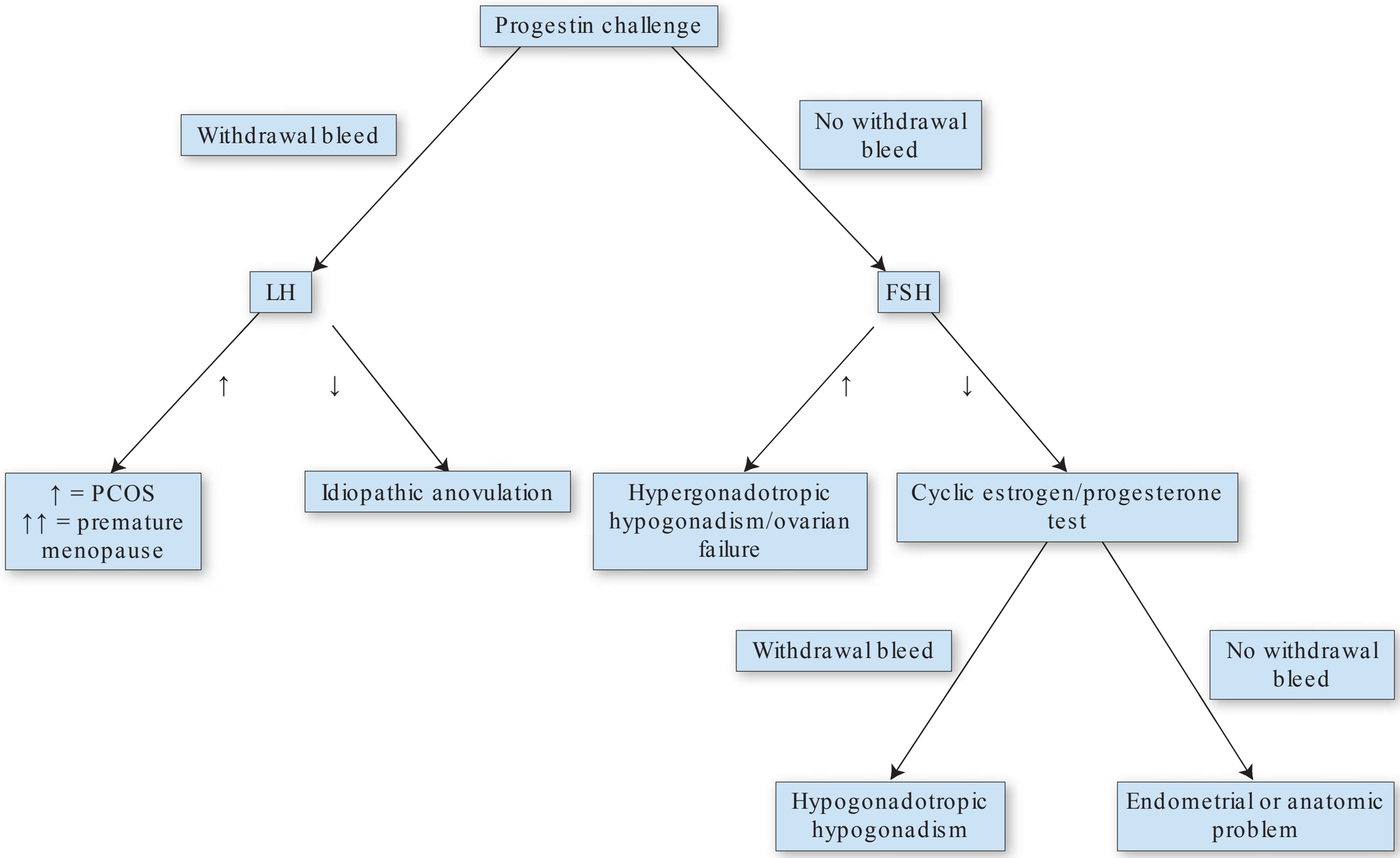


FIGURE 2.12-4. Workup of 2° amenorrhea.

1° DYSMENORRHEA

Menstrual pain associated with ovulatory cycles in the absence of pathologic findings. Caused by uterine vasoconstriction, anoxia, and sustained contractions mediated by an excess of prostaglandin ($PGF_{2\alpha}$).

History/Pe

- Presents with low, midline, spasmodic pelvic pain that often radiates to the back or inner thighs.
- Cramps occur in the first 1–3 days of menstruation and may be associated with nausea, diarrhea, headache, and flushing.
- There are **no pathologic findings on pelvic exam.**

Diagnosis

A diagnosis of exclusion. Rule out 2° dysmenorrhea (see below).

Treatment

NSAIDs; topical heat therapy; combined OCPs, progestin IUD.

2° DYSMENORRHEA

Menstrual pain for which an organic cause exists. Common causes include endometriosis and adenomyosis, fibroids, adhesions, and PID.

1 A

The most likely diagnosis is menopause. As a clinical diagnosis, menopause does not require the ordering of any tests. However, if you are trying to rule it out as a cause of 2° amenorrhea, you may consider ordering an FSH level. Elevation is suggestive of menopause.

2 A

The most likely diagnosis is pregnancy. Confirm with a β-hCG.

History/Pe

- Patients may have a palpable uterine mass, cervical motion tenderness, adnexal tenderness, or vaginal or cervical discharge. However, normal abdominal and pelvic exams do not rule out pathology.
- See Table 2.12-5 for distinguishing features of endometriosis vs adenomyosis.

KEY FACT

Polyps are **not** associated with pain.

Diagnosis

- Obtain a β-hCG to exclude ectopic pregnancy.
- Order the following:
  - CBC with differential to rule out infection or neoplasm.
  - UA to rule out UTI.
  - Gonococcal/chlamydial swabs to rule out STDs/PID.
- Look for pelvic pathology causing pain (see Table 2.12-5).

Treatment

Treatment is etiology specific.

ABNORMAL UTERINE BLEEDING

- Normal menstrual bleeding ranges from 2 to 7 days. Abnormal uterine bleeding refers to alterations in quantity, duration, or frequency. Classified by acronym PALM-COEIN.

TABLE 2.12-5. Endometriosis vs Adenomyosis

Variable	Endometriosis	Adenomyosis
Definitio	Functional endometrial glands and stroma **outside** the uterus.	Endometrial tissue **in** the myometrium of the uterus.
History/PE	**Cyclic** pelvic and/or rectal pain and dyspareunia. Uterus **not** enlarged but **painful nodules, restricted range of motion.**	Classic triad of pain, **menorrhagia,** and an **enlarged, boggy, symmetric** uterus.
Diagnosis	Requires direct visualization by **laparoscopy** or laparotomy. Classic lesions have a blue-black ("raspberry") or dark brown ("powder-burned") appearance. The ovaries may have endometriomas ("chocolate cysts").	**MRI** can aid in diagnosis but is costly. Ultrasonography is useful but cannot always distinguish between leiomyoma and adenomyosis. Ultimately a pathologic diagnosis.
Treatment	**Pharmacologic:** Inhibit ovulation. Combination OCPs (first line), GnRH analogues (leuprolide), danazol, NSAIDs, or progestins. **Conservative surgical treatment:** Excision, cauterization, or ablation of the lesions and lysis of adhesions. Twenty percent of patients can become pregnant subsequent to treatment. **Definitive surgical treatment:** TAH/BSO ± lysis of adhesions.	**Pharmacologic:** Largely symptomatic relief. NSAIDs (first line) plus OCPs or progestins. **Conservative surgical treatment:** Endometrial ablation or resection using hysteroscopy. Complete eradication of deep adenomyosis is difficult and results in ↑ treatment failure. **Definitive surgical treatment:** Hysterectomy is the only definitive treatment.
Complications	Infertility (the most common cause among menstruating women > 30 years of age).	May rarely progress to endometrial carcinoma.

KEY FACT

Postmenopausal vaginal bleeding is cancer until proven otherwise.

KEY FACT

Pregnancy is the most common cause of abnormal uterine bleeding and amenorrhea. Always check a pregnancy test!

KEY FACT

First-line treatment of abnormal uterine bleeding consists of NSAIDs to ↓ blood loss!

KEY FACT

OCPs and the Mirena IUD are highly effective treatment options for menorrhagia.

- **PALM** refers to structural causes: **P**olyp, **A**denomyosis, **L**eiomyoma, and **M**alignancy/hyperplasia.
- **COEIN** refers to nonstructural causes: **C**oagulopathy, **O**vulatory dysfunction, **E**ndometrial, **I**atrogenic, and **N**ot yet classified.

History/Pe

Assess the extent of bleeding:

- **Oligomenorrhea:** An ↑ length of time between menses (35–90 days between cycles).
- **Polymenorrhea:** Frequent menstruation (< 21-day cycle); anovular.
- **Menorrhagia:** ↑ amount of flow (> 80 mL of blood loss per cycle) or prolonged bleeding (flow lasting > 8 days); may lead to anemia.
- **Metrorrhagia:** Bleeding between periods.
- **Menometrorrhagia:** Excessive and irregular bleeding.
- On pelvic examination, look for an enlarged uterus, a cervical mass, or polyps to assess for myomas, pregnancy, or cervical cancer.

Diagnosis

- **β-hCG:** To rule out pregnancy.
- **CBC:** To evaluate for anemia.
- **Pap smear:** To rule out cervical cancer.
- **Gonorrhea/chlamydia probe:** To rule out cervical bleeding from cervicitis.
- **TFTs and prolactin**: To rule out hyper-/hypothyroidism and hyperprolactinemia.
- **Platelet count, PT/PTT:** To rule out von Willebrand disease and factor XI deficiency, primarily in adolescent patients.
- **Ultrasonography:** To look for uterine masses, polycystic ovaries, and thickness of the endometrium.
- Endometrial biopsy should be performed:
  - If the endometrium is ≥ 4 mm in a **postmenopausal woman, or**
  - If the patient is > 35 years of age with risk factors for endometrial hyperplasia (eg, obesity, diabetes).

Treatment

- **Acute heavy bleeding:**
  - High-dose estrogen IV stabilizes the endometrial lining and typically stops bleeding within 1 hour. Transition to combined oral contraceptive or add progestin when bleeding stabilized.
  - If estrogen is contraindicated, can give high dose progestin therapy alone.
  - If bleeding is not controlled within 12–24 hours, a D&C is often indicated.
- **Ovulatory bleeding:**
  - NSAIDs to ↓ blood loss.
  - Tranexamic acid can be given for 5 days during menses.
  - If the patient is hemodynamically stable, give OCPs, oral or injectable progestin, or insert a progestin IUD.
- **Anovulatory bleeding:**
  - The goal is to convert proliferative endometrium to secretory endometrium (to ↓ the risk of endometrial hyperplasia/cancer).
  - Progestins × 10 days to stimulate withdrawal bleeding.
  - OCPs.
  - Progestin IUD.

- If medical management fails:
  - **D&C.**
  - **Hysteroscopy:** To identify endometrial polyps or to perform directed uterine biopsies.
  - **Uterine fibroid embolization:** If fibroids are the cause of menorrhagia.
  - **Hysterectomy or endometrial ablation:** Appropriate for the following:
    - Women for whom hormonal treatment fails or who do not want it.
    - Women who no longer desire fertility.
    - Women who have symptomatic anemia and/or who experience a disruption in their quality of life from persistent, unscheduled bleeding.

KEY FACT

Complications of abnormal uterine bleeding are anemia and endometrial hyperplasia ± carcinoma.

Reproductive Endocrinology

CONGENITAL ADRENAL HYPERPLASIA

A deficiency of at least one enzyme required for the biochemical synthesis of cortisol from cholesterol (see Figure 2.12-5 and Table 2.12-6). Includes the following:

- **21-hydroxylase deficiency:** Accounts for ~ 90% of CAH cases; "classic" form is most severe and presents as a newborn infant girl with ambiguous genitalia and adrenal insufficiency (with or without life-threatening salt wasting). "Nonclassic" is a late-onset form that presents with andro-

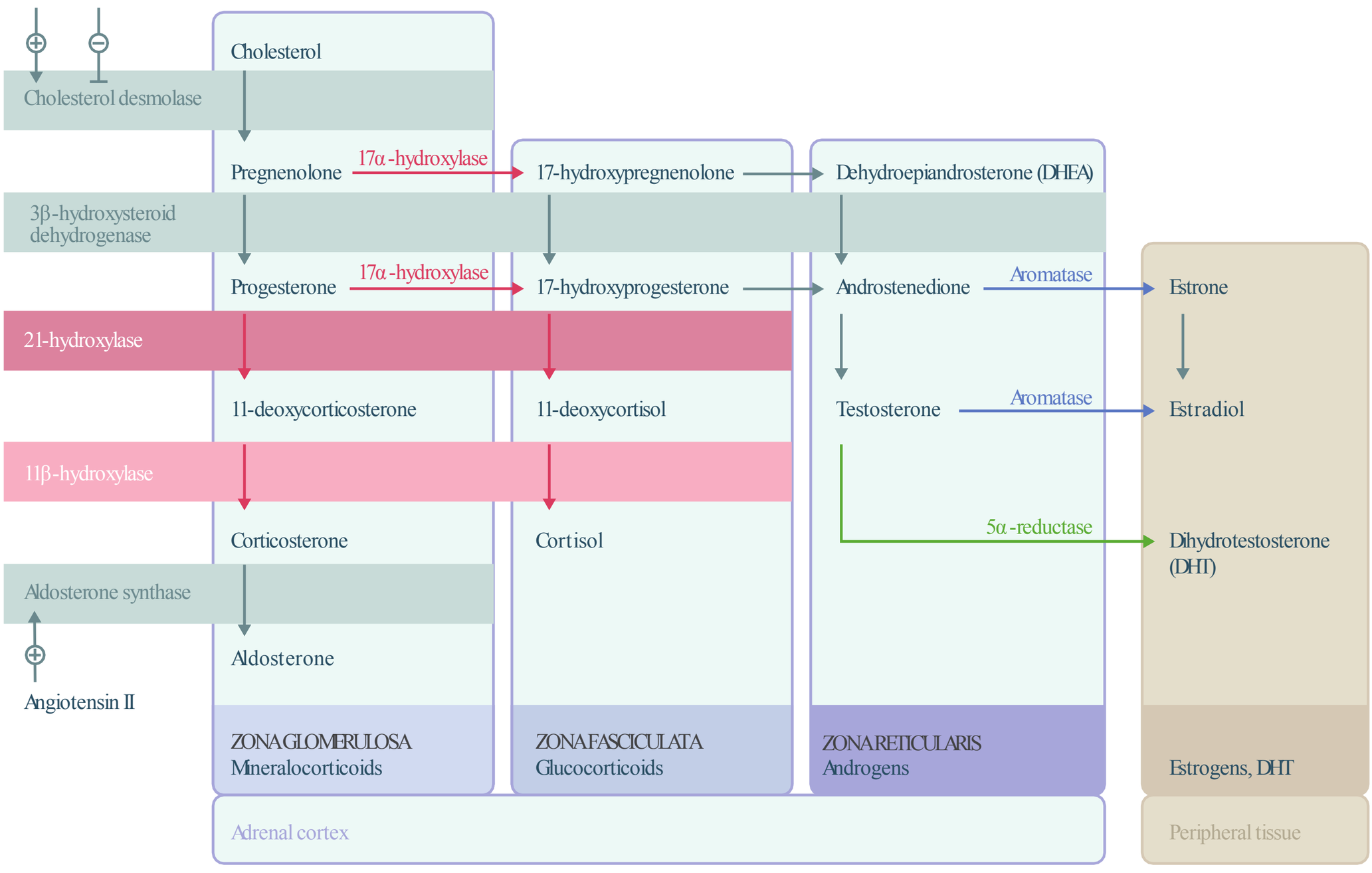


FIGURE 2.12-5. Glucocorticoid biosynthesis pathway. (Modified with permission from USMLE-Rx.com as published in Le Tet al. First Aid for the USMLE Step 1 2015. New York, NY: McGraw-Hill; 2015.)

TABLE 2.12-6. Overview of Congenital Adrenal Hyperplasia

Enzyme deficiency	Mineralocorticoids	Cortisol	Sex hormones	BP	$[K^+]$	Labs	Presentation
17α-hydroxylase[a]	↑	↓	↓	↑	↓	↓ androstenedione	XY: pseudohermaphroditism (ambiguous genitalia, undescended testes) XX: lack secondary sexual development
21-hydroxylase[a]	↓	↓	↑	↓	↓	↑ renin activity ↑ 17-hydroxyprogesterone	Most common Presents in infancy (salt wasting) or childhood (precocious puberty) XX: virilization
11β-hydroxylase[a]	↓ aldosterone ↑ 11-deoxycorticosterone (results in ↑ BP)	↓	↑	↑	↓	↓ renin activity	XX: virilization

[a]All congenital adrenal enzyme deficiencies are characterized by an enlargement of both adrenal glands due to ↑ ACTH stimulation (due to ↓ cortisol).

Reproduced with permission from Le T et al. First Aid for the USMLE Step 1 2015. New York, NY: McGraw-Hill; 2015.

KEY FACT

- Hirsutism = male hair pattern.
- Virilization = frontal balding, muscularity, clitoromegaly, and deepening of the voice.
- Defeminization = ↓ breast size; loss of feminine adipose tissue.

KEY FACT

21-hydroxylase deficiency can present with **hypo**tension, whereas 11β-hydroxylase and 17-hydroxylase deficiencies can present with **hyper**tension due to accumulation of deoxycorticosterone.

gen excess or could be asymptomatic. Cannot convert 17-hydroxyprogesterone to 11-deoxycortisol → ↓ cortisol synthesis → ↑ adrenal stimulation → ↑ ACTH and androgens.

- **11β-hydroxylase deficiency:** Second most common cause of adrenal hyperplasia. Cannot convert 11-deoxycortisol to cortisol or 11-deoxycorticosterone to corticosterone, also leading to ↑ ACTH and androgens.

History/Pe

Androgen excess: Genital ambiguity, premature pubarche, menstrual irregularity, infertility, hirsutism, acne, and, rarely, a palpable pelvic mass.

Diagnosis

- Physical exam.
- **21-hydroxylase deficiency:** ↑ **17-OH progesterone** levels: substrate for 21-hydroxylase (often part of neonatal screening).
- Cosyntropin stimulation test is gold standard, but not necessary if ↑↑ 17-OH.
- **11β-hydroxylase deficiency:** ↑ serum 11-deoxycortisol and 11-deoxycorticosterone.
- **Both:** Next, in order of importance can assess for elevated: cortisol, androstenedione (also consider adrenal/ovarian neoplasm), and DHEA (also consider adrenal neoplasm, Cushing syndrome).
- **If salt wasting:** Will also have ↓ aldosterone, ↓ sodium, ↑ potassium, and ↑ renin associated with hypovolemia.

Treatment

- **Glucocorticoids** (eg, dexamethasone). Medical therapy for adrenal and ovarian disorders prevents new terminal hair growth but does not resolve hirsutism.
- Add **mineralocorticoid therapy** (eg, **fludrocortisone**) if salt wasting.
- Laser ablation, electrolysis, or conventional hair removal techniques must be used to remove unwanted hair.

POLYCYSTIC OVARIAN SYNDROME

PCOS has a prevalence of 6–10% among US women of reproductive age and is the most common cause of infertility in women. Syndrome of excess testosterone and excess estrogen. Diagnosis requires fulfillment of two of the following three (Rotterdam criteria):

1. Polycystic ovaries (via ultrasonography).
2. Oligo- and/or anovulation.
3. Clinical and/or biochemical evidence of hyperandrogenism.

History/Pe

Common presentation: Obesity (BMI > 30 kg/m^2), menstrual cycle disturbances, infertility, acne, androgenic alopecia, and hirsutism from hyperandrogenism.

Women with PCOS are also at ↑ risk for the following:

- DM2: Acanthosis nigricans.
- Metabolic syndrome—insulin resistance, atherogenic dyslipidemia, and hypertension.

Diagnosis

- **Biochemical testing of hyperandrogenemia:** ↑ testosterone.
  - ↑ free testosterone more sensitive than total testosterone (total can be normal), due to low sex hormone-binding globulin.
- **Exclude other causes of hyperandrogenism:**
  - DHEA-S to rule out adrenal tumor.
  - Pelvic ultrasound to rule out androgen secreting ovarian tumor.
  - 17-OH progesterone to rule out nonclassical CAH.
  - Consider screening in the setting of clinical signs of Cushing syndrome (eg, moon facies, buffalo hump, abdominal striae) or acromegaly (eg, ↑ head size).
- **Evaluate for metabolic abnormalities:**
  - Two-hour oral glucose tolerance test.
  - Fasting lipid and lipoprotein levels (total cholesterol, HDL, LDL, triglycerides).
- **Optional tests:** Not necessary if both oligomenorrhea and signs of hyperandrogenism are present.
  - **Transvaginal ultrasonography:** Look for **more than eight** small, subcapsular follicles forming a **"pearl necklace" sign** (see Figure 2.12-6). Seen in roughly two-thirds of women with PCOS.
  - **Gonadotropins: ↑ LH/FSH ratio** (> 2:1).
  - **24-hour urine for free cortisol:** Adult-onset CAH or Cushing syndrome.

KEY FACT

The most severe form of PCOS is **HAIR-AN syndrome: H**yper**A**ndrogenism, **I**nsulin **R**esistance, and **A**canthosis **N**igricans.

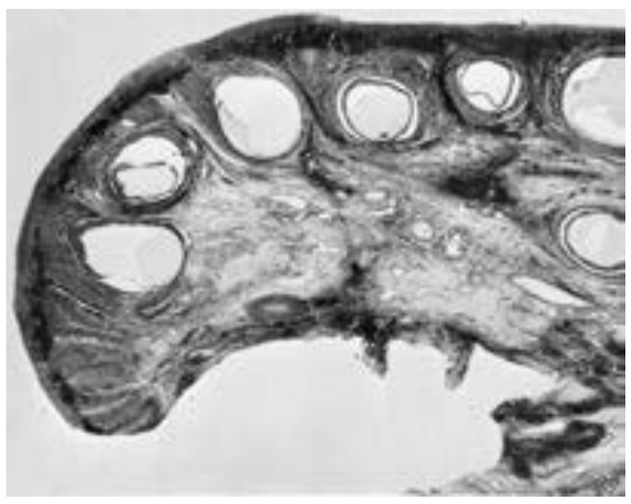


FIGURE 2.12-6. Polycystic ovary with prominent multiple cysts. (Reproduced with permission from DeCherney AH, Nathan R. Current Diagnosis & Treatment: Obstetrics & Gynecology, 10th ed. New York, NY: McGraw-Hill; 2007.)

Q 1

A 28-year-old woman comes to clinic for a wellness exam. She describes that approximately 2 weeks after her menses, she experiences intense, sharp lower quadrant abdominal pain that lasts a couple of hours. The pain varies from the right to the left side each cycle. What is the name of this phenomenon?

Q 2

A 23-year-old woman presents with fever and abdominal pain of 2 days' duration. She has a ⊕ chandelier sign. Antibiotics are started. What is the next step in management?

Treatment

- **Women who are not attempting to conceive:** Treat with a combination of OCPs, progestin ± **metformin** (or other insulin-sensitizing agents).
- **Women who are attempting to conceive:** Clomiphene (selective estrogen receptor modulator) ± metformin is first-line treatment for ovulatory stimulation.
- **Symptom-specific treatment:**
  - **Hirsutism:** Combination OCPs are first line; antiandrogens (spironolactone, finasteride) and metformin may also be used.
  - **Obesity, cardiovascular risk factors, lipid levels:** Diet, weight loss (can also help regulate ovulation), and exercise plus potentially lipid-controlling medication (eg, statins).

KEY FACT

Combined hormonal contraception or progestin ↓ the risk of endometrial hyperplasia/carcinoma among women with PCOS.

Complications

↑ risk of early-onset DM2; ↑ risk of miscarriages; ↑ long-term risk of breast and endometrial cancer due to unopposed estrogen secretion.

KEY FACT

Female causes are more common than male causes in infertility. Begin with history (including menstrual) and physical exam of woman, then semen analysis before further workup in woman, as it is simple and noninvasive.

INFERTILITY

- The inability to conceive after 12 months of normal, regular, unprotected sexual activity.
- 1° infertility is characterized by no prior pregnancies; 2° infertility occurs in the setting of at least one prior pregnancy. Etiologies are shown in Figure 2.12-7 and Table 2.12-7.

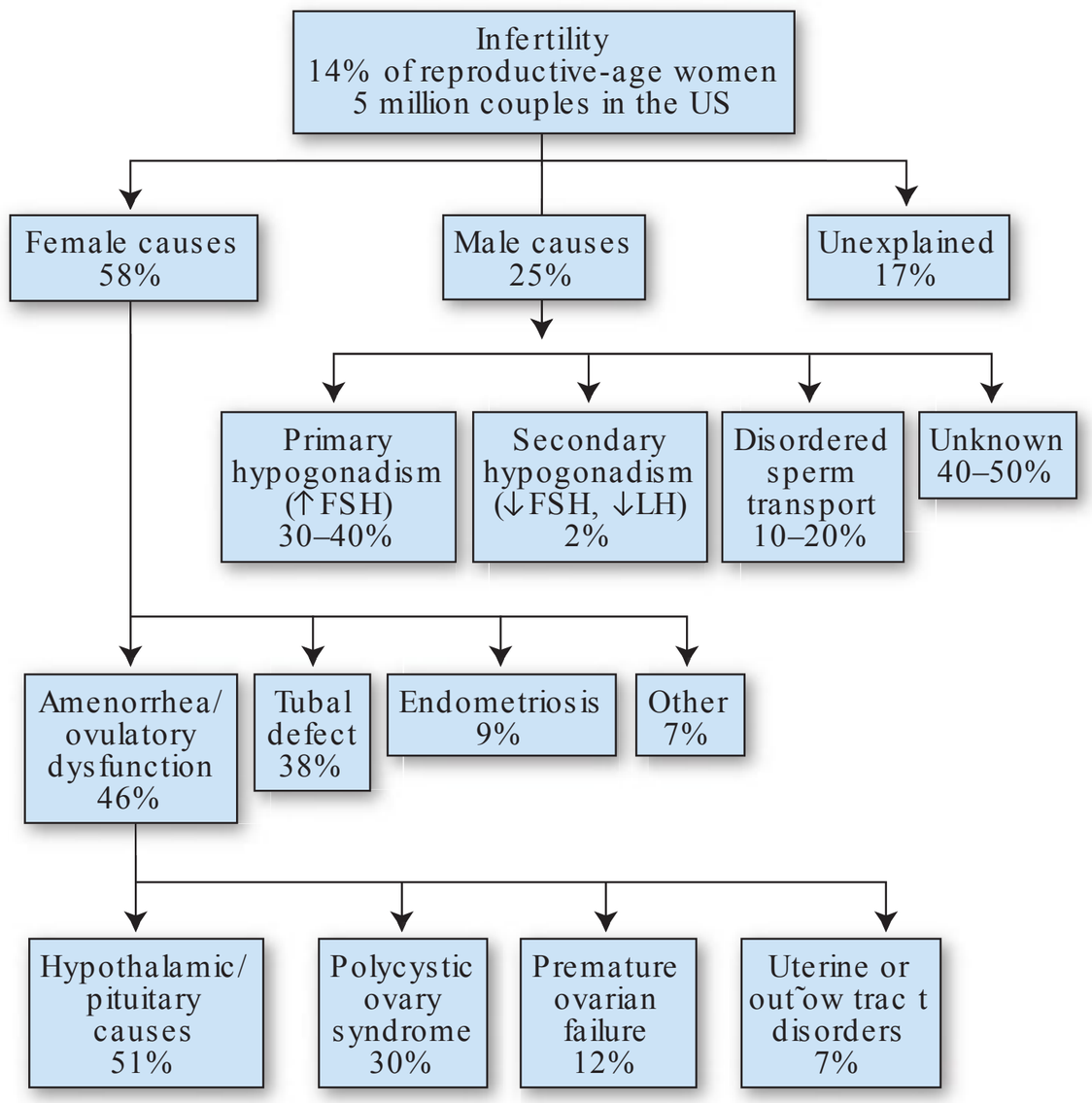


FIGURE 2.12-7. Causes of infertility. (Reproduced with permission from Fauci AS et al. Harrison's Principles of Internal Medicine, 17th ed. New York, NY: McGraw-Hill; 2008.)

1 A

This is called mittelschmerz, pain at ovulation due to progesterone production. It can switch sides depending on which ovary ovulates in a given cycle.

2 A

Pelvic ultrasonography to rule out tubo-ovarian abscess.

TABLE 2.12-7. Infertility Workup

etiology	history/pe	diagnosis	treatment
Male causes	Testicular injury or infection. Medications (corticosteroids, cimetidine, spironolactone). Thyroid or liver disease. Signs of hypogonadism. Varicocele.	Semen analysis. TSH. Prolactin. Karyotype (to rule out Klinefelter syndrome).	Treatment of hormonal deficiency. Intrauterine insemination (IUI). Donor insemination. IVF. Intracytoplasmic sperm injection.
Ovulatory factors	Age (incidence ↑ with age). Symptoms of hyper-/hypothyroidism. Galactorrhea. Menstrual cycle abnormalities.	Menstrual history. Basal body temperature. Ovulation predictor. Midluteal progesterone. Early follicular FSH ± estradiol level (ovarian reserve). TSH, prolactin, androgens. Ovarian sonography (antral follicle count). Endometrial biopsy (luteal-phase defect).	Treatment depends on the etiology (eg, levothyroxine, dopamine). Induction of ovulation with **clomiphene,** gonadotropins, and pulsatile GnRH. IUI. IVF.
Tubal/pelvic factors	History of PID, appendicitis, endometriosis, pelvic adhesions, tubal surgery.	Hysterosalpingogram. Endometrial biopsy.	Laparoscopic resection or ablation of endometriomas or fibroids. IVF.
Cervical factors	Cryotherapy, conization, or DES exposure in utero.	Pap smear. Physical examination. Antisperm antibodies.	IUI with washed sperm. IVF.
Uterine factors	Polyps. Fibroids. Congenital anomalies.	Ultrasound. Sonohysterogram. Hysterosalpingogram.	Surgical treatment.

Gynecologic Infections

CYST AND ABSCESS OF BARTHOLIN DUCT

In cyst formation, the gland duct is obstructed while mucus produced by the gland continues to accumulate, resulting in cystic dilatation. An obstructed Bartholin duct that becomes infected can develop an abscess that is polymicrobial.

History/Pe

- Cysts: 1–3 cm in size, unilateral, and often asymptomatic. If larger, lead to periodic, painful swelling and dyspareunia. Diagnosis is clinical: Mass at **medial labia majora** or **lower vestibular area** on physical exam.
- Abscess: Extremely painful, warm, fluctuant mass in same location as above, possible cellulitis.

Treatment

- **Asymptomatic cysts:** No therapy ± warm soaks. Consider drainage and biopsy if > 40 years old to exclude carcinoma.
- **Abscess:** Aspiration or incision and drainage to prevent reaccumulation; test for gonorrhea and Chlamydia and other pathogens.
- Antibiotics are unnecessary unless cellulitis or STI present.

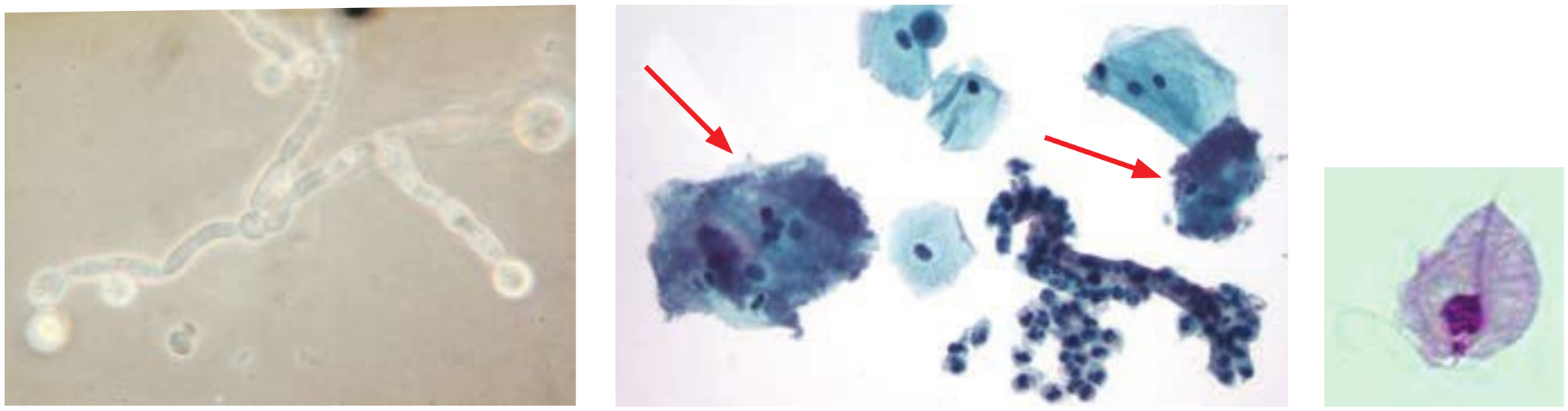
VAGINITIS

A spectrum of conditions that cause vulvovaginal symptoms such as itching, burning, irritation, and abnormal discharge. The most common causes are bacterial vaginosis, vulvovaginal candidiasis, and trichomoniasis (see Table 2.12-8).

TABLE 2.12-8. Causes of Vaginitis

Variable	Bacterial Vaginosis	Trichomonas	Yeast
Incidence	15–50% (most common).	5–50%.	15–30%.
Etiology	**Not** an infection: shift in vaginal flora (↑ anaerobes, ↓ lactobacilli).	Protozoal flagellates **(an STD).**	Usually Candida albicans.
Risk factors	Pregnancy, multiple sexual partners, female sexual partner, frequent douching.	Unprotected sex with multiple partners.	**DM, antibiotic use, pregnancy, corticosteroids,** HIV, OCP use, ↑ frequency of intercourse, tight-fitting clothing.
History	Odor, ↑ discharge.	↑ discharge, odor, pruritus, dysuria.	Pruritus, dysuria, burning, ↑ discharge.
Exam	Mild vulvar irritation.	"Strawberry petechiae" in the upper vagina/cervix.	Erythematous, excoriated vulva/vagina.
Discharge	Homogeneous, **grayish-white, fishy**/stale odor.	Profuse, malodorous, **yellow-green, frothy.**	Thick, white, curdy texture without odor.
Wet mount[a]	**"Clue cells"** (epithelial cells coated with bacteria; see Figure 2.12-8); "No clue why I smell fish in the vagina garden."	**Motile trichomonads** (flagellated organisms that are slightly larger than WBCs). See Figure 2.12-8.	—
KOH prep	⊕ "whiff" test (fishy smell).	—	**Pseudohyphae** (see Figure 2.12-8).
Treatment	PO or vaginal metronidazole or vaginal clindamycin.	Single-dose PO metronidazole or tinidazole. Treat partners, otherwise a "ping-pong effect"; test for other STDs.	Topical azole or PO fluconazole.
Complications	Chorioamnionitis/endometritis, infection, preterm delivery, miscarriage, PID.	Same as for bacterial vaginosis.	

[a]If there are many WBCs and no organism on saline smear, suspect Chlamydia.



A B C

FIGURE 2.12-8. Causes of vaginitis. (A) Candidal vaginitis. Candida albicans organisms are evident on KOH wet mount. **(B)** Gardnerella vaginalis. Note the granular epithelial cells ("clue cells") and indistinct cell margins. **(C)** Trichomonas vaginalis. Trophozoites (motile) on wet mount; "strawberry cervix." (Part A reproduced with permission from Wolff K et al. Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology, 5th ed. New York, NY: McGraw-Hill; 2005. Part B reproduced with permission from USMLE-Rx.com. Part C reproduced courtesy of the US Department of Health and Human Services.)

History/PE

- Presents with a change in discharge, malodor, pruritus, irritation, burning, swelling, dyspareunia, and dysuria.
- Normal secretions are as follows:
  - **Midcycle estrogen surge:** Clear, elastic, mucoid secretions.
  - **Luteal phase/pregnancy:** Thick and white secretions; adhere to the vaginal wall.
- Conduct a thorough examination of the vulva, vaginal walls, and cervix.
- If there are many WBCs and no organism on saline smear, suspect Chlamydia.

Diagnosis/Treatment

- Vaginal fluid for vaginal pH, amine (whiff) test, wet mount (with saline), and 10% potassium hydroxide (KOH) microscopy.
- If purulent discharge, numerous leukocytes on wet prep, cervical friability, and any symptoms of PID, order DNA tests or cultures for Neisseria gonorrhoeae or Chlamydia trachomatis to rule out cervicitis.
- Treatment is etiology specific (see Table 2.12-8).

CERVICITIS

- **Inflammation of the uterine cervix.** Etiologies are as follows:
  - **Infectious** (most common): Chlamydia, gonococcus, Trichomonas, HSV. Chlamydia trachomatis is more common than gonococcus in mucopurulent cervicitis.
  - **Noninfectious:** Trauma, radiation exposure, malignancy.
- **Hx/PE:** Yellow-green mucopurulent discharge; ⊕ cervical motion tenderness; absence of other signs of PID.
- **Dx/Tx:** See the discussion of STDs in the Infectious Disease chapter. If mucopurulent: **Empiric treatment for both** C trachomatis **and** N gonorrhoeae.

PELVIC INFLAMMATORY DISEASE

A polymicrobial infection of the upper genital tract. Associated with N gonorrhoeae (one-third of cases), C trachomatis (one-third of cases), and endoge-

KEY FACT

Criteria for the clinical diagnosis of bacterial vaginosis (three of four are required):

- Abnormal whitish-gray discharge
- Vaginal pH > 4.5
- ⊕ amine (whiff) test
- Clue cells comprise > **20%** of epithelial cells on wet mount

KEY FACT

Genital ulcers: Treponema pallidum cause single **painless** chancre, Haemophilus ducreyi cause **deep** painful ulcers with irregular borders (you "do cry"), and HSV causes multiple **shallow** painful ulcers.

Q

A 20-year-old woman is diagnosed with trichomonas and prescribed an antibiotic. She calls her physician complaining of flushing, nausea, and emesis. What antibiotic was the patient prescribed and what should she have been warned of?

KEY FACT

The chandelier sign is defined as severe cervical motion tenderness that makes the patient "jump for the chandelier" on examination.

MNEMONIC

Acute causes of pelvic pain—

A ROPE

Appendicitis—periumbilical → RLQ pain, fever, nausea, vomiting.
Ruptured ovarian cyst—recent strenuous physical activity, minor vaginal bleeding.
Ovarian torsion and abscess—unilateral pain, nausea, vomiting, and gradual onset of fever, vaginal discharge, respectively.
PID—gradual onset of fever, vaginal discharge.
Ectopic pregnancy—rule out with β-hCG test.

KEY FACT

Mild and subclinical PID is a major cause of tubal factor infertility, ectopic pregnancy, and chronic pelvic pain due to pelvic scarring.

nous aerobes/anaerobes. Risk factors include non-Caucasian ethnicity, douching, smoking, multiple sex partners, and prior STDs and/or PID.

History/Pe

- Presents with lower abdominal pain, fever, chills, menstrual disturbances, and purulent cervical discharge.
- Cervical motion tenderness (chandelier sign) and adnexal tenderness.

Diagnosis

- Diagnosed by the presence of acute lower abdominal or pelvic pain plus one of the following:
  - Uterine tenderness.
  - Adnexal tenderness.
  - Cervical motion tenderness.
- First, order a β-hCG to rule out pregnancy.
- A WBC count > 10,000 cells/μL has **poor positive and negative predictive value** for PID.
- Ultrasonography may show thickening or dilation of the fallopian tubes, fluid in the cul-de-sac, a multicystic ovary, or tubo-ovarian abscess.

Treatment

- Antibiotic treatment should not be delayed while awaiting culture results. All sexual partners should be examined and treated appropriately.
- **Outpatient regimens:**
  - **Regimen A:** Ceftriaxone IM × one dose **or** cefoxitin **plus** probenecid **plus** doxycycline × 14 days ± metronidazole × 14 days.
  - **Regimen B:** Ofloxacin **or** levofloxacin × 14 days ± metronidazole × 14 days. Only in special cases given ↑ quinolone-resistant N gonorrhoeae.
- **Inpatient antibiotic regimens:**
  - Cefoxitin or cefotetan plus doxycycline × 14 days.
  - Clindamycin plus gentamicin × 14 days.
- **Surgery:**
  - Drainage of a tubo-ovarian/pelvic abscess is appropriate if the mass persists after antibiotic treatment; the abscess is > 4–6 cm; or the mass is in the cul-de-sac in the midline and drainable through the vagina.
  - If the patient's condition deteriorates, perform exploratory laparoscopy or laparotomy.
  - Surgery may range from TAH/BSO with lysis of adhesions in severe cases to conservative surgery for women who desire to maintain fertility.

Complications

- Repeated episodes of infection, chronic pelvic pain, dyspareunia, and ectopic pregnancy.
- Infertility (10% after the first episode, 25% after the second episode, and 50% after a third episode).
- Fitz-Hugh–Curtis syndrome (presents with associated perihepatitis, RUQ pain, abnormal liver function, and referred right shoulder pain).

A

She was prescribed metronidazole. She should have been warned to stay away from alcohol while taking it, as it causes a disulfiram-like reaction.

TOXIC SHOCK SYNDROME

Caused by preformed Staphylococcus aureus **toxin (TSST-1);** can occur within 5 days of using **tampons.** The incidence in menstruating women is now 6–7/100,000 annually. Nonmenstrual cases are nearly as common as menstrual cases (eg, surgical, burns).

History/Pe

- **Presents with abrupt onset of fever, vomiting, and watery diarrhea.**
- A diffuse macular erythematous rash is also seen.
- Nonpurulent conjunctivitis is common.
- Desquamation, **especially of the palms and soles,** generally occurs during recovery within 1–2 weeks of illness.

Diagnosis

Based on clinical presentation: Fever > 38.9°C, hypotension, skin findings, involvement of three or more organ systems. Blood cultures are ⊖, given that it's caused by a **preformed toxin** and not invasive properties of the organism.

Treatment

- **Rapid rehydration,** examination for foreign objects in vaginal canal, drainage if localized infection found.
- **Empiric antibiotics:** Clindamycin + vancomycin.
- If methicillin-sensitive S aureus isolated in wound: Clindamycin + oxacillin OR nafcillin.
- If methicillin-resistant S aureus isolated: Clindamycin + vancomycin OR linezolid.

Complications

- The mortality rate associated with TSS is 3–6%.
- Causes of death include cardiac arrhythmias, cardiomyopathy, respiratory failure due to ARDS, and coagulopathy due to DIC.

KEY FACT

TSS is a rare but potentially fatal reaction to Saureus toxin. Diagnosis is clinical, because the reaction is to the toxin, not to the bacterium itself. The first steps in treatment are rapid rehydration and antibiotic treatment.

Gynecologic Neoplasms

Gynecologic cancers include uterine, endometrial, ovarian, cervical, and vulvar neoplasms. Ovarian cancer carries the highest mortality.

UTERINE LEIOMYOMA (FIBROIDS)

The most common **benign** neoplasm of the female genital tract. They present as discrete, round, firm, and often multiple tumors composed of smooth muscle and connective tissue.

- Fibroids are hormone sensitive, size will ↑ in pregnancy and ↓ after menopause.
- Malignant transformation to leiomyosarcoma is rare (0.1–0.5%).
- Prevalence: More common in black (50%) than white (25%) women.

KEY FACT

Uterine myomas are benign but can cause infertility or menorrhagia. Key words on physical exam: Uterus is irregular and mobile.

History/Pe

- The majority of cases are asymptomatic.
- Symptomatic patients may present with the following:
  - **Bleeding:** Longer, heavier periods; anemia.
  - **Mass effect:** Pelvic/rectal pressure constipation, and urinary frequency or retention.
  - **Pain:** 2° dysmenorrhea, dyspareunia.
  - **Pelvic symptoms:** A firm, nontender, irregular enlarged ("lumpy-bumpy"), or cobblestone uterus may be felt on physical examination.

KEY FACT

If a uterine mass continues to grow after menopause, suspect malignancy.

Diagnosis

- **Physical exam.**
- **Ultrasonography (transvaginal):** To look for uterine myomas; can also exclude ovarian masses. Calcification indicates necrosis.
- **MRI:** Can delineate intramural, subserosal, and submucous myomas. Best modality for visualization, usually reserved in preparation for surgery, **or** if concerned for leiomyosarcoma (new or growing mass in postmenopausal woman).
- **CBC:** To assess for anemia.

Treatment

- **If asymptomatic:** Expectant management with annual pelvic exams and CBCs as needed.
- **Pharmacologic:**
  - Combined hormonal contraception.
  - Medroxyprogesterone acetate or danazol to slow or stop bleeding.
  - GnRH analogues (leuprolide or nafarelin) to ↓ the size of myomas, suppress further growth, and ↓ surrounding vascularity. Also used prior to surgery.
  - NSAIDs for pain.
- **Surgery:**
  - **Women of childbearing years:** Abdominal or hysteroscopic myomectomy.
  - **Women who have completed childbearing:** Total or subtotal abdominal or vaginal hysterectomy.
  - **Uterine artery embolization** (~ 25% will need further invasive treatment).
  - Emergent surgery may be required if torsion of a pedunculated myoma.

Complications

Infertility may be due to a myoma that distorts the uterine cavity and plays a role similar to that of an IUD.

ENDOMETRIAL CANCER

KEY FACT

Vaginal bleeding is present in 80% of women with endometrial carcinoma, but only 5–10% of women with abnormal vaginal bleeding have endometrial cancer.

Type I endometrioid adenocarcinomas derive from **atypical endometrial hyperplasia** and are the most common female reproductive cancer in the United States. Type II cancers derive from serous or clear cell histology (see Table 2.12-9). Although type II cancers tend to be more aggressive, diagnosis and management are similar for both types.

History/Pe

- Vaginal bleeding (early finding).
- Pain (late finding).
- Metabolic syndrome.

Diagnosis

- First, physical exam and pregnancy test if premenopausal.
- Second, ultrasonography. If postmenopausal, can do transvaginal and evaluate endometrial stripe (< 4 mm unlikely to be endometrial cancer). Shows thickened endometrium with hypertrophy and neoplastic change (Figure 2.12-9).
- Finally, endometrial/endocervical biopsy. If postmenopausal and any bleeding, must perform a biopsy regardless of ultrasonography results.

KEY FACT

Hormonal contraceptives are protective against endometrial cancer.

TABLE 2.12-9. Types of Endometrial Cancer

Variable	Type I: Endometrioid	Type II: Serous
Epidemiology	75% of endometrial cancers.	25% of endometrial cancers.
Etiology	Unopposed estrogen stimulation (eg, tamoxifen use, exogenous estrogen-only therapy).	Unrelated to estrogen; the p53 mutation is present in 90% of cases.
Precursor lesion	Hyperplasia and atypical hyperplasia.	None.
Mean age at diagnosis	55 years.	67 years.
Prognosis	Favorable.	Poor.

Treatment

- High-dose progestins for women of childbearing age.
- TAH/BSO ± radiation for postmenopausal women.
- TAH/BSO with adjuvant chemotherapy for advanced-stage cancer.

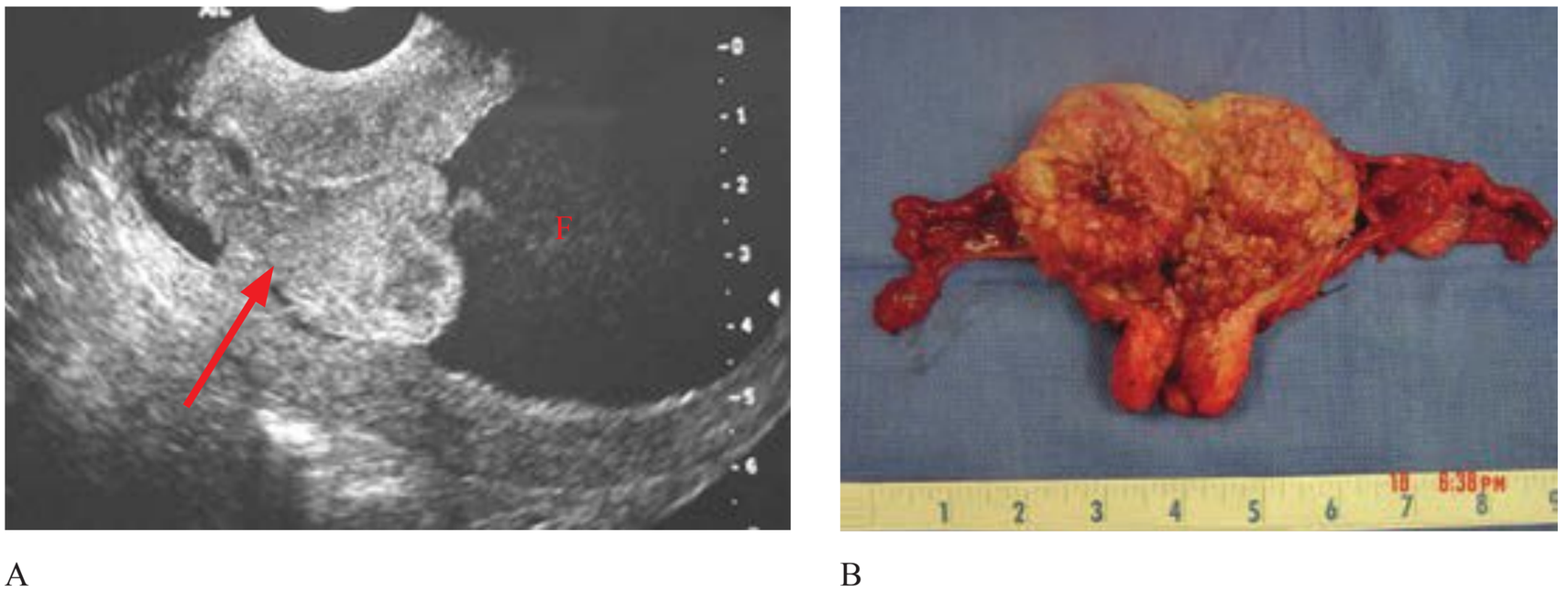
CERVICAL CANCER

The endocervix lies proximal to the external os, is non-visible, and is composed of columnar cells (similar to the lower uterine segment). The ectocervix is visible and composed of squamous cells (similar to the vagina). The exposure of columnar cells to an acidic vaginal pH results in metaplasia to squamous cells. The normal squamocolumnar junction (transformation zone) is located in the ectocervix and can be exposed to carcinogens, resulting in cervical intraepithelial neoplasia (CIN), an abnormal proliferation or overgrowth of the basal cell layer.

KEY FACT

When to perform a biopsy for endometrial cancer:

- Postmenopausal: Any bleeding, spotting.
- Premenopausal: Sustained intermenstrual bleeding, menorrhagia, or amenorrhea after initial workup and in the setting of unopposed estrogen (obesity, DM).



A B

FIGURE 2.12-9. Endometrial cancer. (A) Sagittal endovaginal ultrasonogram demonstrates a mass (arrow) in the lower uterine segment endometrial canal, with fluid (F) distending the canal in the fundus. **(B)** Gross specimen from a different patient shows a large mass filling the endometrial canal and invading the myometrium. (Part A reproduced with permission from USMLE-Rx.com. Part B reproduced with permission from Schorge JO et al. Williams Gynecology. New York, NY: McGraw-Hill; 2008.)

- Human papillomavirus (HPV) DNA is found in 99.7% of all cervical carcinomas. HPV 16 is the most prevalent type in squamous cell carcinoma; HPV 18 is most prevalent in adenocarcinoma.
- Additional risk factors for cervical cancer include immunosuppression, infection with HIV or a history of STDs, tobacco use, high parity, and OCPs.
- The Gardasil vaccine may protect against HPV types 6, 11 (cause 90% of genital warts) and 16, 18 (cause 70% of cervical cancer). Recommended to be given up until age 26.

KEY FACT

Fifty percent of women with cervical cancer had not had a Pap smear in the 3 years preceding their diagnosis, and another 10% had not been screened in 5 years.

History/Pe

- Metrorrhagia, postcoital spotting, and cervical ulceration are the most common signs.
- A bloody or purulent, malodorous, nonpruritic discharge may appear after invasion.

Screening

- The American Congress of Obstetricians and Gynecologists (ACOG) currently recommends that screening for cervical cancer begin at age 21 regardless of onset of sexual activity.
- Screening recommendations for women with previously normal exams:
  - < 21 years: No screening.
  - 21–29 years: Every 3 years perform Pap smear (cytology).
  - 30–65 years: Every 3 years perform Pap smear **or** every 3 years perform Pap smear or every 5 years perform co-testing (Pap smear + HPV test).
  - 65 years: Stop screening if prior tests were negative.
  - See Table 2.12-10 for classification systems of Pap smears.

TABLE 2.12-10. Classification of Pap Smears

CIN	Bethesda System
Benign	Negative
Benign with inflammation	ASC-US ASC-H
CIN I	LSIL
CIN II	HSIL
CIN III	HSIL
Invasive cancer	Invasive cancer

CIN is the histologic classification. Bethesda system is used for reporting cytological diagnoses.

KEY FACT

Subtypes of cervical lesions:

- **ASC-US:** Atypical squamous cells of undetermined significance.
- **ASC-H:** Atypical squamous cells—cannot exclude HSIL.
- **LSIL:** Low-grade intraepithelial lesion.
- **AGC:** Atypical glandular cells of undetermined significance.
- **HSIL:** High-grade squamous intraepithelial lesion.

Women with DES exposure (risk for clear cell cancer) and/or immunocompromised status (including HIV positivity) should continue to be screened as long as they do not have a life-limiting condition.

Diagnosis

The diagnosis and follow-up of specific subtypes of cervical lesions should be as follows (these guidelines do not apply to adolescents and pregnant women). Cotesting (HPV test and Pap smear) is routinely done starting at 30 years.

1. Women 21–24 years with cervical cytology showing **atypical squamous cells of undetermined significance (ASC-US) or low-grade squamous intraepithelial lesion (LSIL).**
   - **Repeat cytology at 12 months (preferred):**
     - **If ⊖, ASC-US, or LSIL:** Repeat cytology at 12 months and if ⊖ × 2 then routine screening but if ASC or higher then colposcopy.
     - **If ASC-H, HSIL, atypical glandular cells:** Colposcopy

     OR
   - **Reflex HPV DNA testing (only if ASC-US):**
     - **If ⊖:** Routine screening.
     - **If ⊕:** Follow algorithm above.
2. ASC-US and > 24 years:
   - **Reflex HPV DNA testing (preferred):**
     - **If ⊖:** Cotesting in 3 years.
     - **If ⊕:** Colposcopy.

     OR
   - **Repeat cytology at 12 months.**
     - **If ⊖:** Routine screening.
     - **If ASC-US or higher:** Colposcopy.

3. **ASC-H:** Colposcopy regardless of HPV status.
4. **LSIL: (21–24 years and above).**
   - **If HPV ⊖ (≥ 30 years):** Repeat cotesting at 12 months (preferred).
     - **If ⊖**: Repeat cotesting in 3 years.
     - **If HPV ⊕ or ASC or higher:** Colposcopy.
   - **If no HPV test (24–30 years):** Colposcopy.
   - **If HPV ⊕ (≥ 30 years):** Colposcopy.
   - **If unsatisfactory or no visible lesion:** Endocervical sampling.
   - **If CIN II, III:** See the management of CIN below.
   - **Pregnant women:** Colposcopy preferred but can defer until 6 weeks postpartum.
5. **AGC:**
   - All women with cervical cytology showing AGC should have colposcopy with endocervical sampling.
   - Women > 35 years of age or those with abnormal bleeding raising concern for endometrial neoplasia should have colposcopy with endocervical **and** endometrial sampling.
6. **ASC-H and HSIL in 21–24 years:** Colposcopy and then proceed as follows:
   - **If CIN II, III:** Treatment as below.
   - **If no CIN II, III:** Colposcopy and cytology at 6 month intervals for 2 years.
     - **If ⊖:** × 2 then routine screening.
     - **If HSIL × 1 year:** Biopsy.
7. **HSIL and > 24 years:** Immediate loop electrosurgical excision (not if pregnant) or colposcopy.

Treatment

For **noninvasive disease,** treatment based on biopsy results for noninvasive lesions (stage 0 disease) is as follows:

- **CIN I** preceded by ASC-US, LSIL, or HPV ⊕.
  - The mainstay of treatment is **follow-up.**
  - Cotesting at 12 months (or cytology if < 30).
    - If ASC or higher or HPV ⊕: Colposcopy.
    - If two ⊖ tests: Resume routine screening.
- **CIN I** preceded by ASC-H or HSIL.
- **Cotesting** (or cytology if < 30) at 12 and 24 months.
  - **If HPV and cytology ⊖:** Resume routine screening.
  - **If HPV ⊕ or abnormal cytology** other than HSIL: Colposcopy.
  - **If HSIL:** Diagnostic excision procedure (unless 21–24 or pregnant).

  OR
- Diagnostic excision procedure (unless 21–24 years or pregnant).
- **CIN I, age 21–24:**
  - **After ASC-US, LSIL:** Repeat cytology at 12 months.
  - **If < ASC-H or HSIL:** Repeat cytology at 12 months.
  - **If ASC-H or higher:** Colposcopy.
- **CIN II and III:**
  - **Ablation:** Cryotherapy or laser ablation, or
  - **Excision:** LEEP; laser and cold-knife conization.
  - **In young women:** Can observe with colposcopy and cytology at 6 and 12 months.
- Postablative or excisional therapy follow-up is as follows:
  - **CIN I, II, or III with ⊖ margins:** Pap smear at 12 months and/or HPV testing.
  - **CIN II or III with ⊕ margins:** Pap smear at 6 months; consider a repeat endocervical curettage.

Treatment based on biopsy results for **invasive disease** is as follows (for staging, see Figure 2.12-10):

- **Microinvasive carcinoma (stage IA1):** Treat with cone biopsy and close follow-up or simple hysterectomy.
- **Stages IA2, IB1, IIA:** May be treated either with radical hysterectomy with concomitant radiation therapy and chemotherapy or with radiation therapy plus chemotherapy alone.
- **Stages IB2, IIB, III, IV:** Treat with radiation therapy plus concurrent cisplatin-based chemotherapy.

Prognosis

- The overall 5-year relative survival rate for carcinoma of the cervix is 68% in Caucasian women and 55% in black women.
- Survival rates are inversely proportionate to the stage of cancer:
  - **Stage 0:** 99–100%.
  - **Stage IA:** > 95%.
  - **Stage IB–IIA:** 80–90%.
  - **Stage IIB:** 65%.
  - **Stage III:** 40%.
  - **Stage IV:** < 20%.
- Almost two-thirds of patients with untreated carcinoma of the cervix die of uremia when ureteral obstruction is bilateral.

VULVAR CANCER

Risk factors include **HPV (types 16, 18, and 31), lichen sclerosus,** infrequent medical exams, diabetes, obesity, hypertension, cardiovascular disease, smoking, high-risk sexual behavior, and immunosuppression. Vulvar intraepithelial neoplasia (VIN) is precancerous and is more commonly found in premenopausal women.

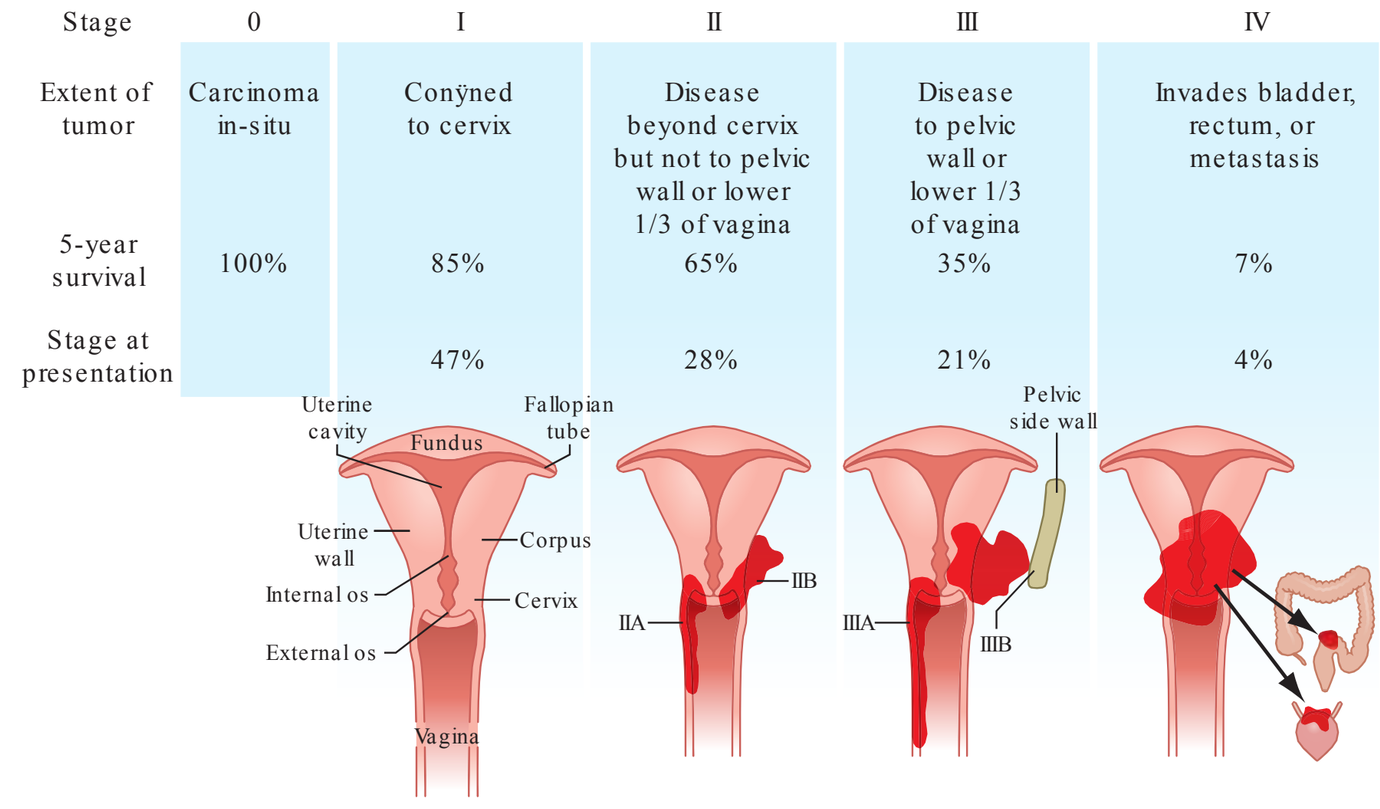


FIGURE 2.12-10. Staging of cervical cancer. Anatomic display of the stages of cervix cancer, defined by location, extent of tumor, frequency of presentation, and 5-year survival. (Reproduced with permission from Fauci AS et al. Harrison's Principles of Internal Medicine, 17th ed. New York, NY: McGraw-Hill; 2008.)

History/Pe

- Presents with pruritus, pain, or ulceration of the mass.
- Additional symptoms include the following:
  - **Early:** Lesions can appear white, pigmented, raised, thickened, nodular, or ulcerative.
  - **Late:** Presents with a large, cauliflower-like or hard ulcerated area in the vulva.

KEY FACT

Lichen sclerosus key words are "atrophic" and "paper-like" skin.

Diagnosis

Vulvar punch biopsy for any suspicious lesions or persistent vulvar pruritus, especially in postmenopausal women.

Treatment

- **High-grade VIN:** Topical chemotherapy, laser ablation, wide local excision, skinning vulvectomy, and simple vulvectomy.
- **Invasive:**
  - Radical vulvectomy and regional lymphadenectomy, or
  - Wide local excision of the 1° tumor with inguinal lymph node dissection ± preoperative radiation, chemotherapy, or both.

VAGINAL CANCER

Accounts for 1–2% of all gynecologic malignancies. Risk factors include immunosuppression, chronic irritation (eg, long-term pessary use or prolapse of female organs), low socioeconomic status, radiation for cervical cancer, hysterectomy for dysplasia, multiple sexual partners, and DES exposure. Etiologies are as follows:

- **Postmenopausal women:** Usually squamous cell carcinoma.
- **Younger women:** Usually other histologic types (eg, adenocarcinoma, clear cell adenocarcinoma from DES).

History/Pe

- Presents with abnormal vaginal bleeding, an abnormal discharge, or postcoital bleeding.
- Found in the upper third of the vagina in 75% of patients.

Diagnosis

Cytology, colposcopy, and biopsy.

Treatment

- Local excision of involved areas when they are few and small.
- Extensive involvement of the vaginal mucosa may require partial or complete vaginectomy.
- Invasive disease requires radiation therapy or radical surgery.

OVARIAN CANCER

Most ovarian tumors are benign, but malignant tumors are the leading cause of death from reproductive tract cancer. Risk factors include the following:

- Age, low parity, ↓ fertility, or delayed childbearing.
- A ⊕ family history. Patients with one affected first-degree relative have a 5% lifetime risk. With two or more affected first-degree relatives, the risk is 7%.

KEY FACT

Frequency of female genital tract cancers: endometrial > ovarian > cervical.
Number of deaths: ovarian > endometrial > cervical.

- The BRCA1 mutation carries a 45% lifetime risk of ovarian cancer. The BRCA2 mutation is associated with a 25% lifetime risk.
- Lynch II syndrome, or hereditary nonpolyposis colorectal cancer (HNPCC), is associated with an ↑ risk of colon, ovarian, endometrial, and breast cancer.
- **OCPs taken for 5 years or more ↓ risk by 29%**

History/Pe

- Both benign and malignant ovarian neoplasms are generally asymptomatic.
- Mild, nonspecific GI symptoms or pelvic pressure/pain may be seen.
- Early disease is typically not detected on routine pelvic exam.
- Some 75% of woman present with advanced malignant disease, as evidenced by abdominal pain and bloating, a palpable abdominal mass, and ascites.
- Table 2.12-11 differentiates the benign and malignant characteristics of pelvic masses.

KEY FACT

Any palpable ovarian or adnexal mass in a premenarchal or postmenopausal patient is suggestive of an ovarian neoplasm.

Diagnosis

- **Tumor markers** (see Table 2.12-12): ↑ **CA-125** is associated with epithelial cell cancer (90% of ovarian cancers) but is used only as a marker for progression and recurrence.
  - **Premenopausal women:** ↑ CA-125 may point to benign disease such as endometriosis.
  - **Postmenopausal women:** ↑ CA-125 (> 35 units) indicates an ↑ likelihood that the ovarian tumor is malignant.
- **Transvaginal ultrasonography:** Used to screen high-risk women and as the first step in the workup of symptomatic women (eg, pelvic fullness, pelvic pain).

TABLE 2.12-11. Benign vs Malignant Pelvic Masses

Finding	benign	Malignant
examination: pelvic Mass		
Mobility	Mobile	Fixed
Consistency	Cystic	Solid or fi m
Location	Unilateral	Bilateral
Cul-de-sac	Smooth	Nodular
transvaginal ultraSonography: adnexal Mass		
Size	< 8 cm	> 8 cm
Consistency	Cystic	Solid or cystic and solid
Septations	Unilocular	Multilocular
Location	Unilateral	Bilateral
Other	Calcific tions	Ascites

Treatment

Treatment of **ovarian masses** is as follows:

- **Premenarchal women:** Masses > 2 cm in diameter require close clinical follow-up and often surgical removal.
- **Premenopausal women:**
  - Observation is appropriate for asymptomatic, mobile, unilateral, simple cystic masses < 8–10 cm in diameter. Most resolve spontaneously.
  - Surgically evaluate masses > 8–10 cm in diameter and those that are complex and/or unchanged on repeat pelvic examination and ultrasonography.
- **Postmenopausal women:**
  - Closely follow with ultrasonography asymptomatic, unilateral simple cysts < 5 cm in diameter with a normal CA-125.
  - Surgically evaluate palpable masses.

Treatment of **ovarian cancer** is as follows:

- **Surgery:**
  - Surgical staging: TAH/BSO with omentectomy and pelvic and paraaortic lymphadenectomy.
  - Benign neoplasms warrant tumor removal or unilateral oophorectomy.
- **Postoperative chemotherapy:** Routine except for women with early-stage or low-grade ovarian cancer.
- **Radiation therapy:** Effective for dysgerminomas.

Prevention

- Women with the BRCA1 gene mutation should be screened annually with ultrasonography and CA-125 testing. Prophylactic oophorectomy is recommended by age 40 or whenever childbearing is completed.
- OCP use ↓ the risk of ovarian cancer.
- There is no routine screening for ovarian cancer.

TABLE 2.12-12. Ovarian Tumor Markers

Tumor	Marker
Epithelial	CA-125
Endodermal sinus	AFP
Embryonal carcinoma	AFP, β-hCG
Choriocarcinoma	β-hCG
Dysgerminoma	LDH
Granulosa cell	Inhibin

Pelvic Organ Prolapse

Risk factors for pelvic organ prolapse include vaginal birth, genetic predisposition, advancing age, prior pelvic surgery (hysterectomy), connective tissue disorders, and ↑ intra-abdominal pressure associated with obesity or straining with chronic constipation.

History/Pe

- Presents with the sensation of a bulge or protrusion in the vagina (see Figure 2.12-11).
- Urinary or fecal incontinence, a sense of incomplete bladder emptying, and/or dyspareunia are also seen.

Diagnosis

The degree of prolapse can be evaluated by having the woman perform the Valsalva maneuver while in the lithotomy position.

Treatment

- Supportive measures include a high-fiber diet and weight reduction in obese patients and limitation of straining and lifting.
- Pessaries may reduce prolapse and are helpful in women who do not wish to undergo surgery or who are chronically ill.
- The most common surgical procedure is vaginal or abdominal hysterectomy with vaginal vault suspension.

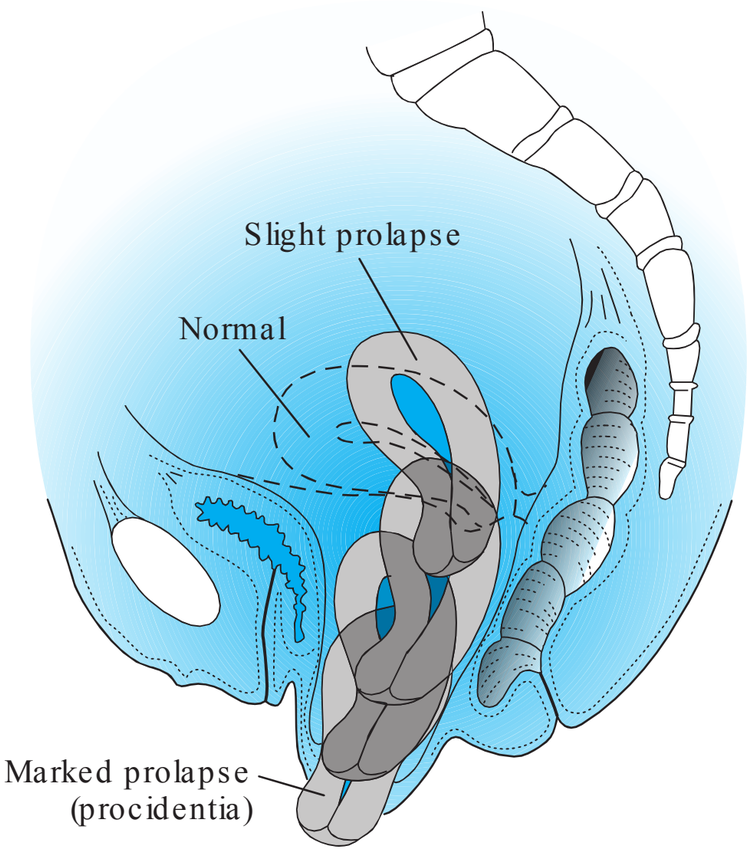


FIGURE 2.12-11. Uterine prolapse. Different degrees of uterine prolapse are illustrated. (Reproduced with permission from DeCherney AH, Nathan L. Current Diagnosis & Treatment Obstetrics & Gynecology, 10th ed. New York, NY: McGraw-Hill; 2007.)

Urinary Incontinence

Defined as the involuntary loss of urine due to either bladder or sphincter dysfunction.

History/Pe

- Table 2.12-13 outlines the types of incontinence along with their distinguishing features and treatment (see also the mnemonic **DIAPPERS**).
- Exclude fistula in cases of total incontinence.
- Look for neurologic abnormalities in cases of urge incontinence (spasticity, flaccidity, rectal sphincter tone) or distended bladder in overflow incontinence.

Diagnosis/Treatment

- Obtain a UA and urine culture to exclude UTI.
- Voiding diary.
- Consider urodynamic testing.
- Serum creatinine to exclude renal dysfunction.
- Obtain a cystogram to demonstrate fistula sites and descensus of the bladder neck.
- Table 2.12-13 outlines treatment options according to subtype.

MNEMONIC

Causes of urinary incontinence without specific ur genital pathology—

DIAPPERS

Delirium/confusional state
Infection
Atrophic urethritis/vaginitis
Pharmaceutical
Psychiatric causes (especially depression)
Excessive urinary output (hyperglycemia, hypercalcemia, CHF)
Restricted mobility
Stool impaction

KEY FACT

Pediatric vaginal discharge may be normal, but STDs resulting from sexual abuse must be ruled out and, if found, reported to Child Protective Services.

Pediatric Gynecology

PEDIATRIC VAGINAL DISCHARGE

Etiologies of vaginal discharge in pediatric patients include the following:

- **Infectious vulvovaginitis:** May present with a malodorous, yellow-green, purulent discharge. Causes include the following:
  - **Group A streptococcus:** The most common infectious cause.

TABLE 2.12-13. Types of Incontinence

Type	History of Urine Loss	Mechanism	Treatment
Total	Uncontrolled loss at all times and in all positions.	Loss of sphincteric efficiency (previous surgery, nerve damage, cancer infiltration). Abnormal connection between the urinary tract and the skin (fistula)	Surgery.
Stress	After ↑ intra-abdominal pressure (coughing, sneezing, lifting).	Urethral sphincteric insufficiency due to **laxity of pelvic floor musculature.** Common in multiparous women or after pelvic surgery.	Kegel exercises and pessary. Vaginal vault suspension surgery.
Urge[a]	Strong, unexpected urge to void that is unrelated to position or activity.	Detrusor hyperreflexia or sphincter dysfunction due to inflammatory conditions or neurogenic disorders of the bladder.	Anticholinergic medications or TCAs; behavioral training (biofeedback).
Overflow[b]	Chronic urinary retention.	Chronically distended bladder with ↑ intravesical pressure that just exceeds the outlet resistance, allowing a small amount of urine to dribble out.	Placement of urethral catheter in acute settings. Treat underlying diseases. Timed voiding.

[a]Etiologies include inhibited contractions, local irritation (cystitis, stone, tumor), and CNS causes.
[b]Etiologies include physical agents (tumor, stricture), neurologic factors (lesions), and medications.

  - Candida: Recent antibiotic therapy, immunosuppressed (eg, diabetes). Rare in children.
  - **STDs:** Typically from sexual abuse.
- **Foreign objects.**
- **Noninfectious vulvovaginitis:** Causes include contact dermatitis and eczema.
- **Sarcoma botryoides (rhabdomyosarcoma):** A malignancy with lesions that have the appearance of "bunches of grapes" within the vagina.

PRECOCIOUS PUBERTY

Onset of 2° sexual characteristics in a child < 8 years of age. Subtypes are as follows (see also Table 2.12-14):

- **Central precocious puberty: Early** activation of hypothalamic GnRH production.
- **Peripheral precocious puberty:** Results from GnRH-independent mechanisms.

History/Pe

- **Signs of estrogen excess** (breast development and possibly vaginal bleeding): Suggest ovarian cysts or tumors.
- **Signs of androgen excess** (pubic and/or axillary hair, enlarged clitoris, and/or acne): Suggest adrenal tumors or CAH.

KEY FACT

If onset of 2° sexual characteristics is seen by age 8, work up for precocious puberty by determining bone age and conducting a GnRH stimulation test to distinguish central from peripheral precocious puberty.

TABLE 2.12-14. Causes of Precocious Pubertal Development

central (gnrh dependent)	peripheral (gnrh independent)
Constitutional (idiopathic)	Congenital adrenal hyperplasia
Hypothalamic lesions (hamartomas, tumors, congenital malformations)	Adrenal tumors
Dysgerminomas	McCune-Albright syndrome (polyostotic fibrous dysplasia)
Hydrocephalus	Gonadal tumors
CNS infections	Exogenous estrogen, oral (OCPs) or topical
CNS trauma/irradiation	Ovarian cysts (females)
Pineal tumors (rare)	
Neurofibromatosis with CNS involvement	
Tuberous sclerosis	

Diagnosis

Figure 2.12-12 illustrates an algorithm for the workup of precocious puberty.

Treatment

- **Central precocious puberty:** Leuprolide is first-line therapy; physical changes regress or cease to progress.
- **Peripheral precocious puberty:** Treat the cause.
  - **Ovarian cysts:** No intervention is necessary, as cysts will usually regress spontaneously.

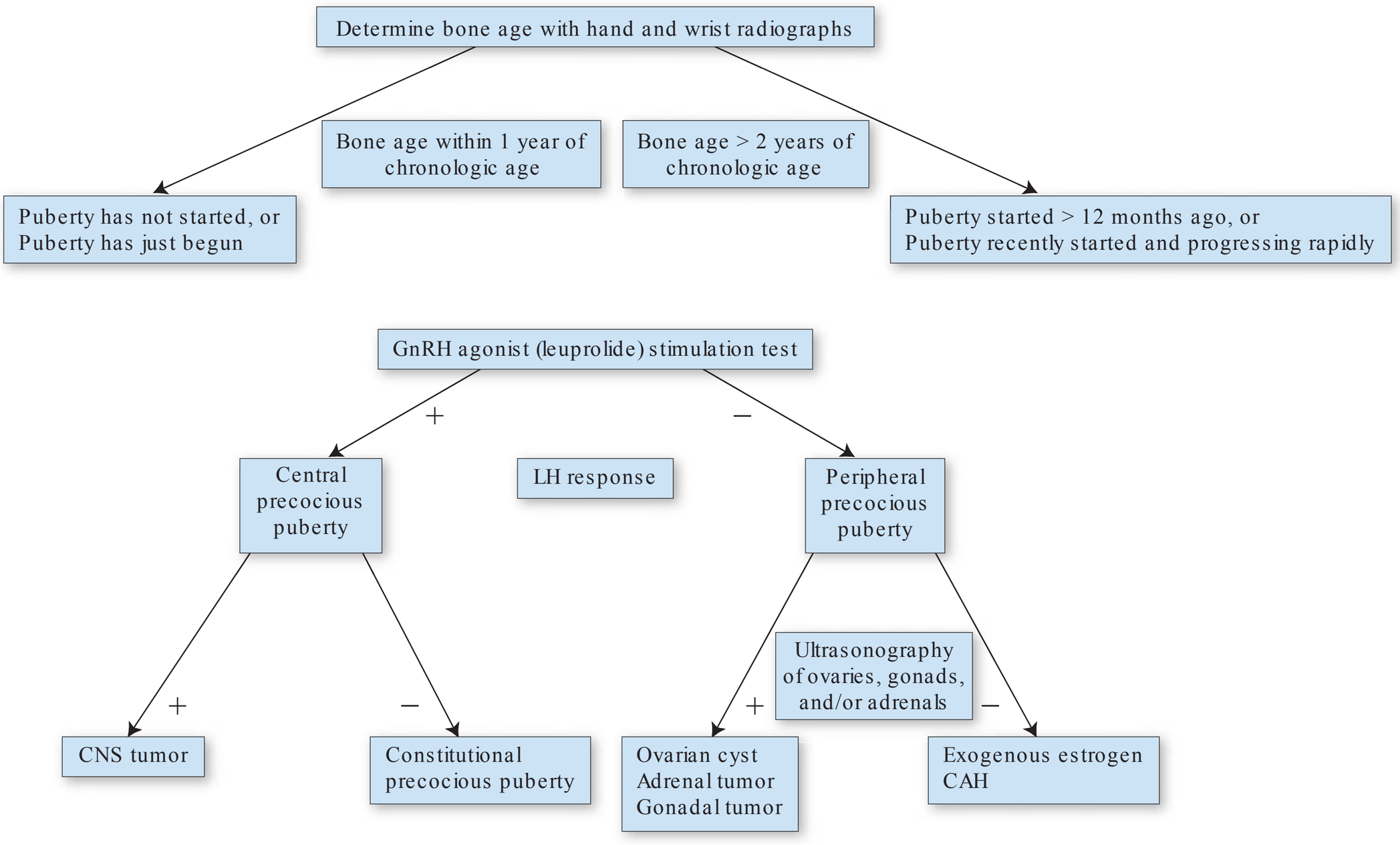


FIGURE 2.12-12. Workup of precocious puberty.

- **CAH:** Treat with glucocorticoids. Surgery is not required for the treatment of ambiguous genitalia.
- **Adrenal or ovarian tumors:** Require surgical resection.
- **McCune-Albright syndrome:** Antiestrogens (tamoxifen) or estrogen synthesis blockers (ketoconazole or testolactone) may be effective.

KEY FACT

A patient with McCune-Albright syndrome presents with precocious puberty, café au lait spots, and bony abnormalities (polyostotic fibrous dysplasia).

Benign Breast Disorders

NONPROLIFERATIVE BREAST LESIONS

Generally no increased risk of breast cancer. Simple breast cysts are the most common, which involves fluid-filled masses from an exaggerated stromal tissue response to hormones and growth factors.

- Findings include cysts (gross and microscopic), papillomatosis, adenosis, fibrosis, and ductal epithelial hyperplasia.
- Primarily affects women 30–50 years of age; rarely found in postmenopausal women.
- Associated with trauma and caffeine use.

History/Pe

- Cyclic bilateral mastalgia and swelling, most prominent just before menstruation.
- Rapid fluctuation in the size of the masses is common.
- Other symptoms include an irregular, bumpy consistency to the breast tissue.

Diagnosis

- See Figure 2.12-13 for an algorithm of a breast mass workup.
- First, have patient return after menstruation, because symptoms fluctuate with hormones.
- If unchanged on follow-up, perform ultrasonography to differentiate a mass from fluid-filled vs solid.
- Next, fine-needle aspiration (FNA) of a discrete mass that is suggestive of a cyst is indicated to alleviate pain as well as to confirm the cystic nature of the mass.
- Excisional biopsy is indicated if no fluid is obtained or if the fluid is bloody on aspiration.
- Mammography is of limited use (especially if < 35 years because of density of breast tissue).
- There is **no** ↑ risk of breast cancer if simple cyst, but ↑ risk if complex cyst (ductal epithelial hyperplasia or cellular atypia), which is rare.

KEY FACT

The differential diagnosis of a breast mass includes fibrocystic disease, fibroadenoma, mastitis/abscess, fat necrosis, and breast cancer.

Treatment

- Reassurance.
- If painful: Aspiration, dietary modifications (eg, caffeine restriction), danazol (rarely used due to side effects of acne, hirsutism, edema), and OCPs (↓ hormonal fluctuations).

PROLIFERATIVE BREAST LESIONS WITHOUT ATYPIA

This includes fibroadenomas, intraductal papillomas, sclerosing adenosis, and usual ductal hyperplasia. Associated with a small increased risk of breast cancer. Intraductal papilloma is composed of papillary cells growing from the

KEY FACT

Intraductal papilloma and mammary duct ectasia are common causes of bloody nipple discharge.

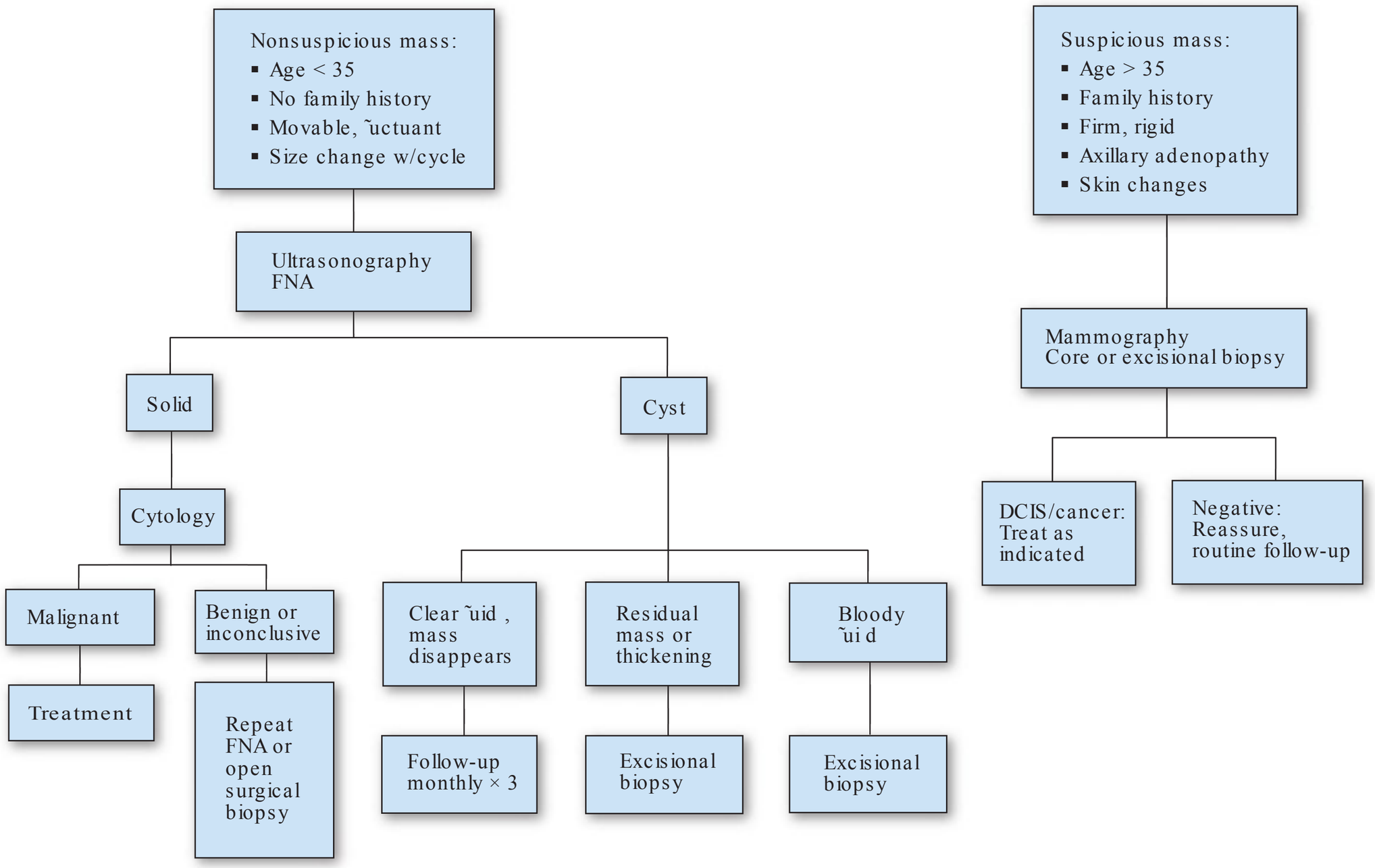


FIGURE 2.12-13. Workup of a breast mass.

wall of a cyst into the lumen. It is diagnosed with core needle biopsy and surgical excision is required since it can be associated with atypia or DCIS. Sclerosing adenosis and usual ductal hyperplasia require no treatment.

FIBROADENOMA

Proliferative breast lesion without atypia. A benign, slow-growing breast tumor with epithelial and stromal components. **The most common breast lesion in women < 30 years of age.**

History/Pe

- Presents as round, rubbery, discrete, relatively mobile mass 1–3 cm in diameter. Generally nontender, but not always.
- Masses are usually solitary, although up to 20% of patients develop multiple fibroadenomas.
- Masses do not change during the menstrual cycle. Note hormonal relationship: can ↑ in size during pregnancy or hormonal therapy and ↓ in size in menopause.

Diagnosis

- Breast ultrasonography to differentiate cystic from solid masses.
- Needle biopsy or FNA.
- Excision with pathologic exam if the diagnosis remains uncertain.

Treatment

Excision is curative, but recurrence is common.

PHYLLODES TUMOR

Phyllodes tumors can sometimes be difficult to distinguish from a fibroadenoma. It is generally larger with greater metastatic ability, and the differentiating features are the papillary projections of the stroma, lined with epithelium and associated with hyperplasia and atypia (Figure 2.12-14).

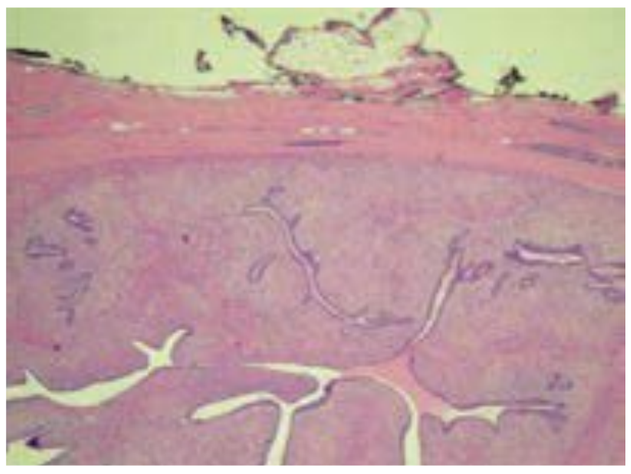


FIGURE 2.12-14. Phyllodes tumor with classic "leaflike" appearance (Reproduced with permission from Crenshaw SA et al. Immediate breast reconstruction with a saline implant and AlloDerm, following removal of a Phyllodes tumor, World J Surg Oncol 2011 Mar 21;9:34.)

ATYPICAL HYPERPLASIA

Atypical hyperplasia (AH) can be ductal or lobular, filling part but not the entire duct or lobule. It is similar to a low-grade DCIS or LCIS with a moderate increased risk of breast cancer. It is a pathologic diagnosis by biopsy often found after a mammogram. AH requires risk reduction, which involves yearly mammograms and tamoxifen or aromatase inhibitor.

Breast Cancer

The most common cancer (affects one in eight women) and the second most common cause of cancer death in women (after lung cancer) in the United States. **Sixty percent occur in the upper outer quadrant.** Risk factors include the following **(half of newly diagnosed patients have risk factors):**

- Female gender; older age; Caucasian.
- A personal history of breast cancer; family history in a first-degree relative; genetic factors (BRCA1 and BRCA2 mutations: associated with early onset).
- Alcohol; cigarettes (controversial).
- Exposure to radiation.
- A history of fibrocystic change with cellular atypia.
- ↑ exposure to estrogen (nulliparity, early menarche, late menopause, first full-term pregnancy after age 35).

KEY FACT

↑ exposure to estrogen (early menarche, late menopause, nulliparity) ↑ the risk of breast cancer.

History/Pe

Clinical manifestations include the following:

- **Early findings:** Single, nontender, immovable, firm-to-hard mass with ill-defined margins **OR** mammographic abnormalities on routine screening.
- **Later findings/locally advanced:** Axillary lymphadenopathy, breast enlargement, pain, peau d'orange skin findings suggesting inflammation (redness, thickening, dimpling), fixation of the mass to the skin or chest wall.
- **Late findings:**
  - Ulceration; supraclavicular lymphadenopathy; edema of the arm.
  - Prolonged unilateral scaling erosion of the nipple with or without discharge (Paget disease of the nipple, specific for ductal carcinoma in situ).
- **Metastatic disease:**
  - Metastases to the bone (pain), lung (dyspnea, cough), and liver (abdominal pain, nausea, jaundice).
  - A firm or hard axillary node > 1 cm.
  - Axillary nodes that are matted or fixed to the skin (stage III); ipsilateral supraclavicular or infraclavicular nodes (stage IV).

KEY FACT

Common metastases to bone: **BLT** with **P**ickle on top: **B**reast, **L**ung, **T**hyroid, **P**rostate.

KEY FACT

In a postmenopausal woman with a new breast lesion, maintain a high degree of clinical suspicion for breast cancer.

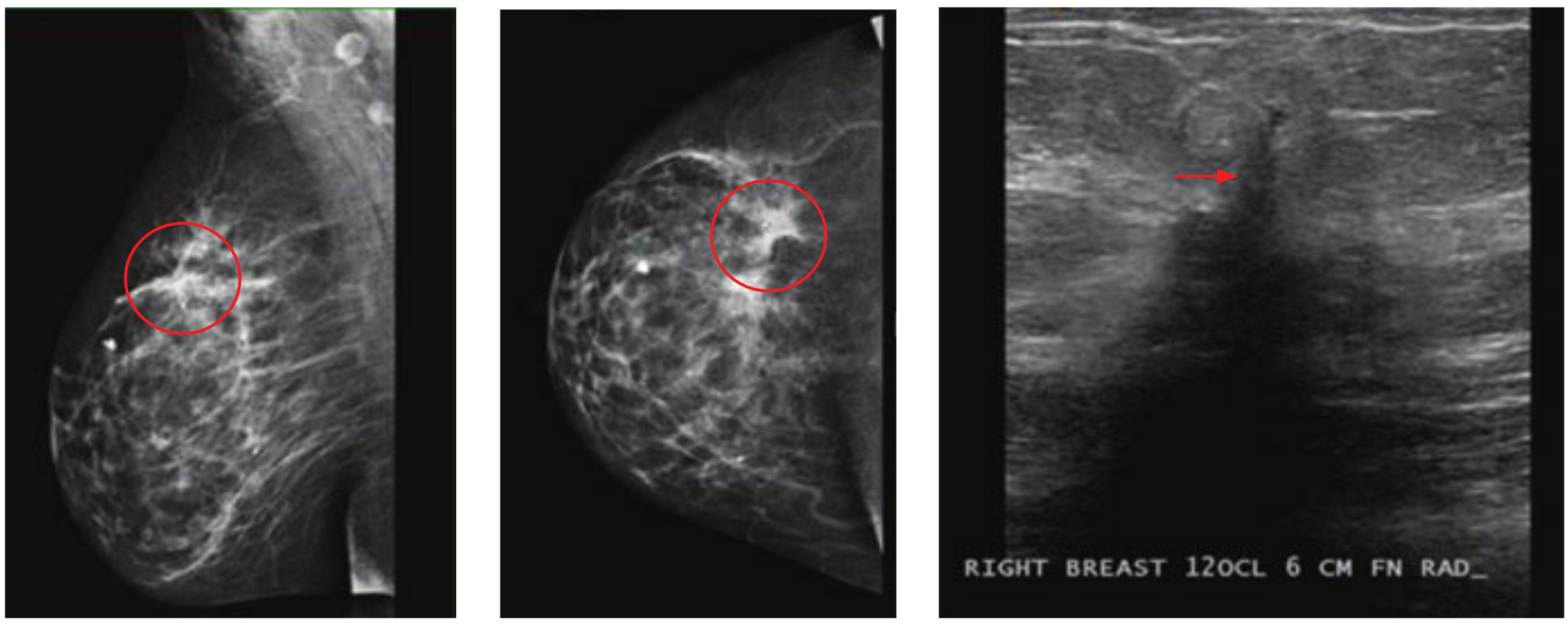
KEY FACT

The first step in the workup of a suspicious mass in postmenopausal women and in those > 30 years of age is a mammogram. For premenopausal women < 30 years of age, get an ultrasonogram.

Diagnosis

Majority of breast cancers diagnosed from mammography.

- **Screening:**
  - **Postmenopausal women: Mammography.** Look for ↑ density with microcalcifications, irregular borders, and spiculated mass. Mammography can detect lesions roughly 2 years before they become clinically palpable (see Figure 2.12-15A).
  - **Premenopausal women: Ultrasonography** for women < 30 years of age due to density of breast tissue; can distinguish a solid mass from a benign cyst (see Figure 2.12-15C).
- **Biopsy of suspicious lesions on mammography:**
  - Perform a mammography-guided FNA or core needle biopsy; full-thickness skin biopsy if signs of inflammation.
  - **FNA:** A good initial biopsy, especially for lesions close to the skin; however, it is a small sample with a high false-⊕ rate. FNA may also be used to follow response to treatment.
  - **Core needle biopsy:** A larger sample that allows testing for receptor status.
  - **Open biopsy:** Less commonly used. Provides tissue for a more accurate diagnosis and allows immediate resection of tumor; however, requires taking the patient to the OR.
- **Receptor status of tumor:** Determine estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor 2 (HER2/neu) status.
- **Tumor markers for recurrent breast cancer:** Include CEA and CA 15-3 or CA 27-29.
- **Metastatic disease:**
  - **Labs:** ↑ ESR, ↑ alkaline phosphatase (liver and bone metastases), ↑ calcium.
  - **Imaging:** CXR; CT of the chest, abdomen, and pelvis; brain MRI. PET and bone scans can also be useful.



A B C

FIGURE 2.12-15. Breast cancer. Mediolateral oblique **(A)** and craniocaudal **(B)** views from a mammogram demonstrate a spiculated mass with a satellite mass (circle) in the central and outer upper right breast. A targeted breast ultrasonogram **(C)** in a different patient demonstrates a hypoechoic mass (arrow) that is taller than it is wide and demonstrates dense posterior acoustic shadowing. (Reproduced with permission from USMLE-Rx.com.)

Treatment

- Early-stage:
  - Breast-conserving surgery + irradiation **or** mastectomy ± radiation (if cancer in deep margins or axillary lymph nodes), both with sentinel node biopsy for evaluation of axillary lymph nodes.
  - Adjuvant therapy as below.
- Locally advanced:
  - Neoadjuvant chemotherapy + trastuzumab if HER2 ⊕ to reduce size for breast conservation.
  - Breast conservation surgery **or** mastectomy with sentinel lymph node biopsy.
  - Adjuvant therapy as below.
- **Adjuvant therapy:**
  - All ER/PR-⊕ patients should receive **tamoxifen** (selective estrogen receptor modulator [SERM] that competitively antagonizes the ER, inhibiting the growth of breast cancer cells) **OR** aromatase inhibitor if postmenopausal (inactivates aromatase that converts peripheral androgens to estrogens).
  - All HER2/neu-⊕ should receive **trastuzumab,** a monoclonal antibody that binds to HER2/neu receptors on the cancer cell.
  - ER, PR, and HER2-⊖ patients should receive **chemotherapy** if tumor > 0.5 cm. Do **not** give if patient already received neoadjuvant therapy.
- **Contraindications to breast-conserving therapy (lumpectomy)** include large tumor size, subareolar location, multifocal tumors, fixation to the chest wall, prior radiation to the chest wall, or involvement of the nipple or overlying skin.
- **Stage IV disease** should be treated with radiation therapy and hormonal therapy; mastectomy may be required for local symptom control.

Table 2.12-15 goes over the breast cancer stages.

Prognosis

- TNM staging (I–IV) is the most reliable indicator of prognosis.
- ER-⊕ and PR-⊕ status is associated with a favorable prognosis.
- Cancer localized to the breast has a 75–90% cure rate. With spread to the axilla, the 5-year survival rate is 40–50%.
- Aneuploidy is associated with a poor prognosis.

Complications

Pleural effusion occurs in 50% of patients with metastatic breast cancer; edema of the arm is common.

TABLE 2.12-15. Breast Cancer Stages

primary tumor (t)	regional lymph nodes (ln)	Metastasis (M)
I: Tumor size < 2 cm	I: Movable ipsi axillary LN	1: Distant mets
II: Tumor size 2–5 cm	II: Fixed ipsi axillary LN	
III: Tumor size > 5 cm	III: Ipsi infra/supraclavicular LN, or clinically detected LN with axillary LN	
IV: Extension: chest wall, skin		

KEY FACT

Breast cancer: stage II is associated with tumor size > 2 cm, stage III is associated with nodal involvement, and stage IV is associated with metastases.

Q 1

A 27-year-old woman palpates a 1 cm × 1 cm new breast mass on self-examination. What is the first step in the workup of the mass?

Q 2

A 30-year-old woman was in a car accident 1 week ago, and subsequently notices a hardened bump in the left breast. What is this likely to be and what can be found on biopsy?

Sexual Assault

The most frequently unreported crime in the United States. Physicians are often required to evaluate sexual assault victims and collect evidence. Most rape victims are women; however, men can also be victims of rape.

History/Pe

- Take a full history, including contraceptive use, last time of coitus, condom use prior to the assault, drug or alcohol use, a history of STDs, a description of the assailant, location and time of the assault, circumstances of the assault (eg, penile penetration, use of condoms, extragenital acts, use or display of weapons), and the patient's actions since the assault (eg, douching, bathing, brushing teeth, urination/defecation, changing clothes).
- Conduct a complete physical examination, making note of any signs of trauma, along with a detailed pelvic examination, including a survey of the external genitals, vagina, cervix, and anus.

Diagnosis

- Gonorrhea and chlamydia smear/culture (including rectal if appropriate); wet mount and culture for trichomonas. On an individual basis, consider serologic testing for HIV, syphilis, HSV, HBV, and CMV.
- Serum pregnancy test.
- Blood alcohol level; urine toxicology screen.

Treatment

- Treat traumatic injuries.
- STD treatment/prophylaxis (ceftriaxone plus azithromycin ± metronidazole); Hep B vaccination if patient has not received full series.
- HIV risk assessment and possible postexposure prophylaxis.
- Emergency contraception for pregnancy prevention.
- Refer for psychological counseling.
- Arrange for follow-up with the same physician or with another provider if more appropriate.
- Follow-up should include repeat screening for STDs, repeat screening for pregnancy, and a discussion of coping methods with appropriate referrals for psychiatric care if needed.

1 A

Ultrasonography. The patient is < 30 years of age, so ultrasonography is the preferred means of distinguishing a solid mass from a cyst.

2 A

This is fat necrosis of the breast. This commonly occurs after trauma that is not always remembered. It is a mimicker of breast cancer in terms of presentation and radiographic findings. Biopsy results differentiate the two and reveal coarse (not micro) calcifications and foamy macrophages.

HIGH-YIELD FACTS IN

PEDIATRICS

Child Abuse 370

Congenital Heart Disease 371
- Septal defects 372
- Patent ductus arteriosus 373
- coarctation of the Aorta 375
- Transposition of the Great Vessels 376
- Tetralogy of Fallot 377

Child Development 378
- developmental Milestones 378
- Growth 380
- Sexual development 380

Genetic Disease 381
- cystic Fibrosis 384

Pediatric Gastroenterological Disease 385
- Intussusception 385
- Pyloric Stenosis 386
- Meckel diverticulum 387
- Hirschsprung disease 387
- Malrotation With Volvulus 388
- Necrotizing Enterocolitis 388

Pediatric Immune-Mediated Disease 389
- Immunodeficiency disorders 389
- Kawasaki disease 392
- Juvenile Idiopathic Arthritis 394

Pediatric Infectious Disease 394
- Acute otitis Media 394
- Bronchiolitis 395
- croup (Laryngotracheobronchitis) 396
- Epiglottitis 397
- Meningitis 397
- ocular Infections of the Neonate 400
- Pertussis (Whooping cough) 400
- Viral Exanthems 401
- Torches Infections 402

Neonatology 403
- Apgar Scoring 403
- congenital Malformations 403
- Neonatal Jaundice 403
- Respiratory distress Syndrome 406

Pediatric Neurologic Disease 407
- cerebral Palsy 407
- Febrile Seizures 408

Pediatric Oncology 409
- Leukemia 409
- Neuroblastoma 410
- Wilms Tumor 411
- childhood Bone Tumors 411

Pediatric Musculoskeletal Disorders 411
- common Pediatric orthopedic Injuries 411
- duchenne Muscular dystrophy 413
- developmental dysplasia of the Hip 414
- Legg-calvé-Perthes disease 415
- Slipped capital Femoral Epiphysis 416
- Scoliosis 416

Well-Child Care 417
- Anticipatory Guidance 417
- Hearing and Vision Screening 418
- childhood Vaccinations 418
- Lead Poisoning 418

Pediatric Urology 419
- Vesicoureteral Reflux 419
- cryptorchidism 420

Child Abuse

Also known as nonaccidental trauma; includes neglect as well as physical, sexual, and psychological maltreatment of children. Suspect abuse if the history is discordant with physical findings or if there is a delay in obtaining appropriate medical care. Certain injuries in children, such as retinal hemorrhages and specific fracture types, are highly suspicious for abuse.

History/Pe

- Suspect abuse if the story is not consistent with the injury pattern or with the child's developmental age. For example, take note if the parents claim that their 2-month-old child "rolled off the couch" (2-month-olds can't roll yet). Also suspect abuse if the story continually changes or is very vague.
- **Risk factors:** Look for parents with a history of alcoholism or drug use, children with complex medical problems, and repeated hospitalizations.
- **Infants:** Abuse or neglect in infants may present as apnea, seizures, feeding intolerance, excessive irritability, somnolence, or failure to thrive (FTT).
- **Older children:** Neglect in older children may present as poor hygiene or behavioral abnormalities.

See Table 2.13-1 **for examination findings.**

Diagnosis

- An **x-ray skeletal survey** and **bone scan** can show fractures in various stages of healing. Radiographs may not show fractures until 1–2 weeks after injury (although they may show evidence of prior trauma in children

KEY FACT

Suspect sexual abuse if there is genital trauma, bleeding, or discharge. In girls, consider vaginal foreign body as an alternative diagnosis, especially in the setting of a foul-smelling vaginal discharge, bleeding, and pain. Also consider if children have an excessive preoccupation/knowledge of adult sexual behaviors.

TABLE 2.13-1. Common Presentations and Mimics of Child Abuse

Type of Abuse	Presentation/Imaging Findings	Mimics
Bruises	Most common physical finding. Often located on head and torso. May be in pattern reflecting implement (hand, belt).	Mongolian spots (see Figure 2.13-1). Coining/cupping (alternative treatments in certain cultures).
Burns	Contact burns: cigarette/curling iron. Immersion burns: hot water, appear on buttocks or stocking-glove distribution.	Scalded skin syndrome, severe contact dermatitis.
Fractures	Spiral fractures: humerus/femur. Epiphyseal-metaphyseal "bucket" fractures. Posterior rib fractures: indicate squeezing.	Osteogenesis imperfecta.
Abusive head trauma	Lethargy, feeding difficulty, apnea, seizures, retinal hemorrhage, subdural/epidural hematoma.	Accidental head trauma.



FIGURE 2.13-1. Mongolian spots. These spots, which are common and are not pathologic in the first few years of life, often resemble bruises. (Reproduced with permission from Wolff Ket al. Fitzpatrick's Dermatology in General Medicine, 7th ed. New York, NY: McGraw-Hill; 2008.)

< 3 years of age); by contrast, bone scans may show fractures within 48 hours.
- If sexual abuse is suspected, test for gonorrhea, syphilis, chlamydia, HIV, and sperm (within 72 hours of assault).
- Rule out abusive head trauma (formerly referred to as shaken baby syndrome) by performing an ophthalmologic exam for **retinal hemorrhages** and a **noncontrast CT** for subdural hematomas. Infants with abusive head trauma often do not exhibit external signs of abuse.
- Consider an **MRI** to visualize white-matter changes associated with violent shaking and the extent of intra- and extracranial bleeds.

Treatment

- Document injuries, including location, size, shape, color, and the nature of all lesions, bruises, or burns.
- Notify Child Protective Services for possible removal of the child from the home.
- Hospitalize if necessary to stabilize injuries or to protect the child.

Congenital Heart Disease

Intrauterine risk factors for congenital heart disease include maternal drug use (alcohol, lithium, thalidomide, phenytoin), maternal infections (rubella), and maternal illness (diabetes mellitus [DM], phenylketonuria [PKU]). Disease is classified by the presence or absence of cyanosis:

- **Acyanotic conditions ("pink babies"):** Have **left-to-right shunts** in which oxygenated blood from the lungs is shunted back into the pulmonary circulation.
- **Cyanotic conditions ("blue babies"):** Have **right-to-left shunts** in which deoxygenated blood is shunted into the systemic circulation.

Table 2.13-2 lists common congenital and other pediatric heart conditions along with their disease associations.

KEY FACT

Neisseria gonorrhoeae isolated on a vaginal culture is definitive evidence of sexual abuse. Chlamydia trachomatis is not, because it can be acquired from the mother during delivery and can persist for up to 3 years.

MNEMONIC

Cyanotic heart defects—

The 5 terrible T's that have right-to-left shunts:

Truncus arteriosus = **1** arterial vessel overriding ventricles.
Transposition of the great vessels = **2** arteries switched.
Tricuspid atresia **(3).**
Tetralogy of Fallot **(4).**
Total anomalous pulmonary venous return = **5** words.

Out of the 5 T's, only **T**ransposition presents with severe cyanosis within the first few hours of life.

Q

A mother presents with her previously healthy 3-month-old infant boy, stating that he has been increasingly difficult to rouse for the past 4 hours and has lost interest in feeding; she left the baby alone with her boyfriend while she left the home to run errands. While en route to the hospital, the baby stopped breathing. Physical examination is notable for occipital bruising. What is the most likely cause of this child's apnea?

KEY FACT

VSD is the most common type of congenital heart disease. They occur most commonly in the membranous septum, and most resolve without intervention.

MNEMONIC

Noncyanotic heart defects—

The 3 D's

VSD
ASD
PDA

KEY FACT

ASD has a fixed, widely split S2.

KEY FACT

ASDs and VSDs rarely present at birth with findings other than harsh systolic murmur. Remember that ASDs, VSDs, and PDAs are acyanotic conditions unless Eisenmenger syndrome has developed (right-to-left shunt, cyanotic).

KEY FACT

In Eisenmenger syndrome, left-to-right shunt leads to pulmonary hypertension and shunt reversal.

A

The most likely cause of this infant's apnea is abusive head trauma, which is most common in 3- to 4-month-old infants and presents early with nonspecific symptoms (lethargy, irritability, poor feeding, vomiting) and later with seizures or apnea. There is generally no reported history of head trauma. Subdural hematoma and edema account for most neurologic findings. In babies with abusive head trauma, there is a 50–70% chance of prior abuse.

TABLE 2.13-2. Pediatric Heart Conditions and Their Disease Associations

Condition	Disorder
ASD and endocardial cushion defects	Down syndrome.
PDA	Congenital rubella.
Coarctation of the aorta	Turner syndrome (many also have bicuspid aortic valve).
Coronary artery aneurysms	Kawasaki disease.
Congenital heart block	Neonatal lupus.
Supravalvular aortic stenosis	Williams syndrome.
Conotruncal abnormalities	Tetralogy of Fallot (overriding aorta), truncus arteriosus, DiGeorge syndrome (tetralogy), velocardiofacial syndrome.
Ebstein abnormality (apical displacement of the tricuspid valve leading to atrialization of the RV)	Maternal lithium use during pregnancy.
Heart failure	Neonatal thyrotoxicosis.
Asymmetric septal hypertrophy and transposition of the great vessels	Maternal diabetes.

SEPTAL DEFECTS

A condition in which an opening in the atrial or ventricular septum allows blood to flow between the atria or ventricles, leading to left-to-right **shunting. Ventricular septal defect (VSD) is the most common type of congenital heart disease.**

Presentation and Diagnosis

See Table 2.13-3.

Treatment

- Most small ASD/VSDs close spontaneously and do not require treatment. Follow-up echocardiography based on size of ASD/VSD and physical exam.
- Antibiotic prophylaxis is generally not recommended prior to procedures.
- Surgical repair is indicated in symptomatic patients who fail medical management, children < 1 year of age with signs of pulmonary hypertension, and older children with large defects that have not ↓ in size over time. Early correction prevents complications such as arrhythmias, right ventricular dysfunction, and Eisenmenger syndrome.
- Treat existing CHF with diuretics (initial treatment), positive inotropes, and angiotensin-converting enzyme inhibitors.

TABLE 2.13-3. Presentation and Diagnosis of ASD vs VSD

	a Sd (Figure 2.13-2)	VSd (Figure 2.13-3)
Associated syndromes	Holt-Oram syndrome (absent radii, ASD, firs -degree heart block). Fetal alcohol syndrome. Trisomy 21.	Apert syndrome (cranial deformities, fusion of the fingers and oes). Down syndrome. Fetal alcohol syndrome. TORCH infections. Cri du chat syndrome. Trisomies (13 and 18).
Presentation	**Small defects:** Asymptomatic. **Large defects:** Easy fatigability; frequent respiratory infection; FTT.	**Small defects:** Asymptomatic. **Large defects:** Recurrent respiratory infections; dyspnea; FTT; CHF.
Auscultation finding	Wide and fi ed split S2. Systolic ejection murmur at the left USB (↑ fl w across pulmonary valve). Mid-diastolic rumble at the left LSB.	Harsh holosystolic murmur at LLSB (louder for small defects). Narrow S2 with ↑ P2 (large defect). Mid-diastolic apical rumble (due to increased fl w across mitral valve).
CXR finding	Cardiomegaly. ↑ pulmonary vascular markings.	
ECG finding	RVH. Right atrial enlargement. PR prolongation is common.	**LVH** (RVH may also be found with large defects).
Echocardiogram finding	Defect and blood fl w across the atrial/ventricular septum.	

PATENT DUCTUS ARTERIOSUS

Failure of the ductus arteriosus to close in the first few days of life, leading to an **acyanotic** left-to-right shunt from the aorta to the pulmonary artery (Figure 2.13-4).

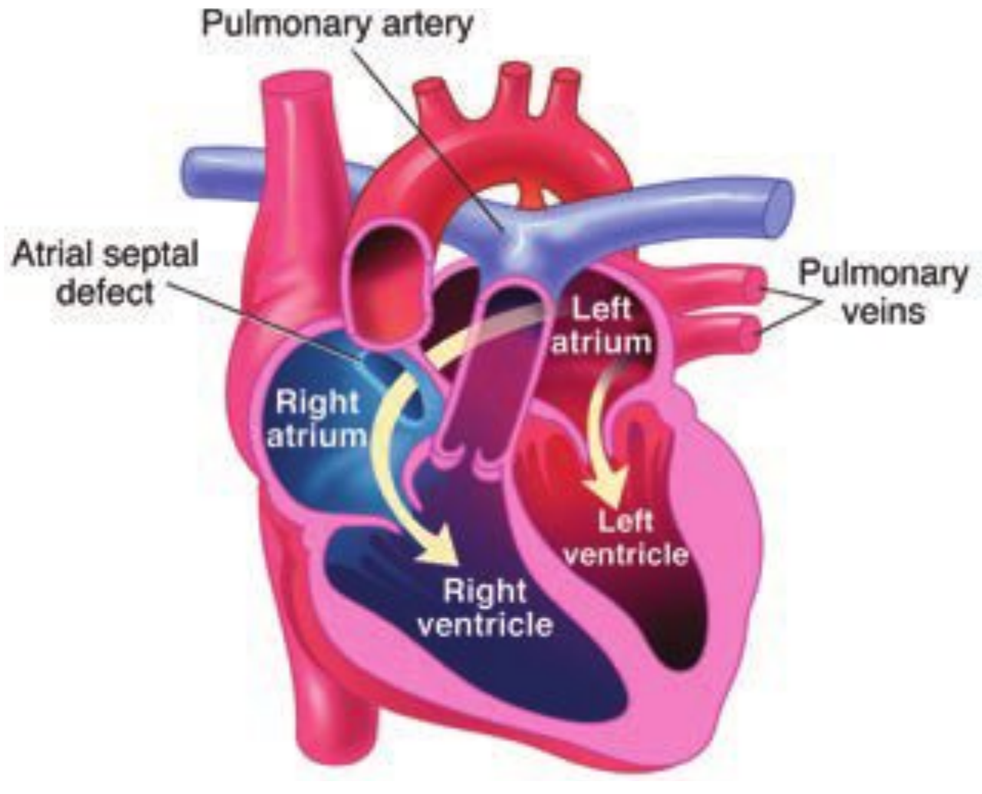


FIGURE 2.13-2. Atrial septal defect with resulting left to right shunt. (Reproduced with permission from USMLE-Rx.com.)

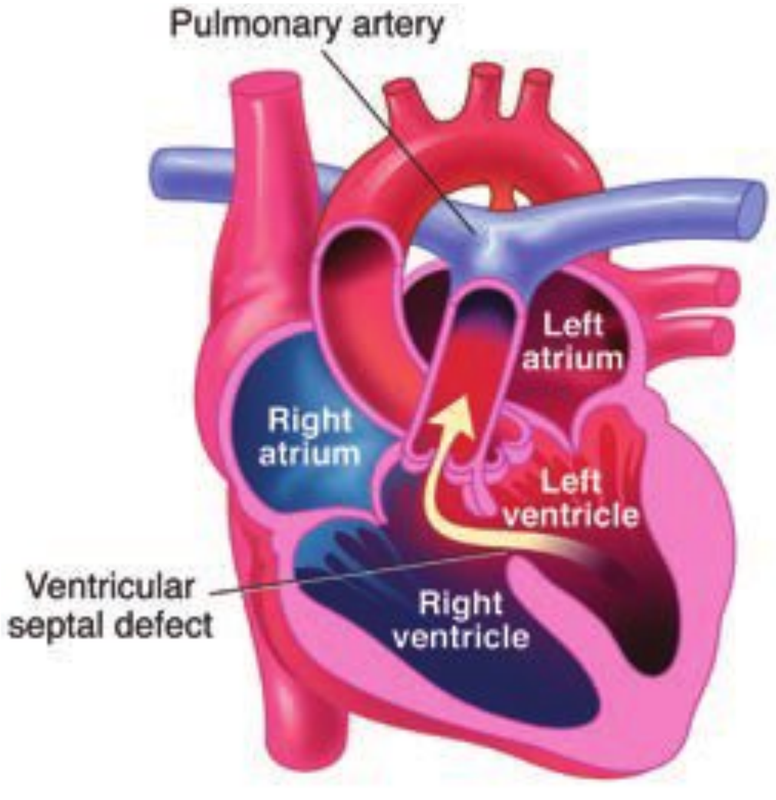


FIGURE 2.13-3. Ventricular septal defect with resultant left-to-right shunt. (Reproduced with permission from USMLE-Rx.com.)

KEY FACT

In infants presenting in a shocklike state within the first few weeks of life, look for:

1. Sepsis.
2. Inborn errors of metabolism.
3. Ductal-dependent congenital heart disease, usually left-sided lesions (as the ductus is closing).
4. Congenital adrenal hyperplasia.

History/Pe

- Typically asymptomatic; patients with large defects may present with FTT, recurrent lower respiratory tract infections, clubbing, and CHF.
- Examination reveals a **continuous "machinery murmur"** at the second left intercostal space at the sternal border, a loud S2, **wide pulse pressure,** and **bounding peripheral pulses.**

Diagnosis

- **Echocardiogram** is the diagnostic test of choice: Color flow Doppler will demonstrate blood flow from the aorta into the pulmonary artery.
- With larger PDAs, echocardiography shows left atrial and left ventricular enlargement.
- ECG may show LVH, and CXR may reveal cardiomegaly if lesions are large.

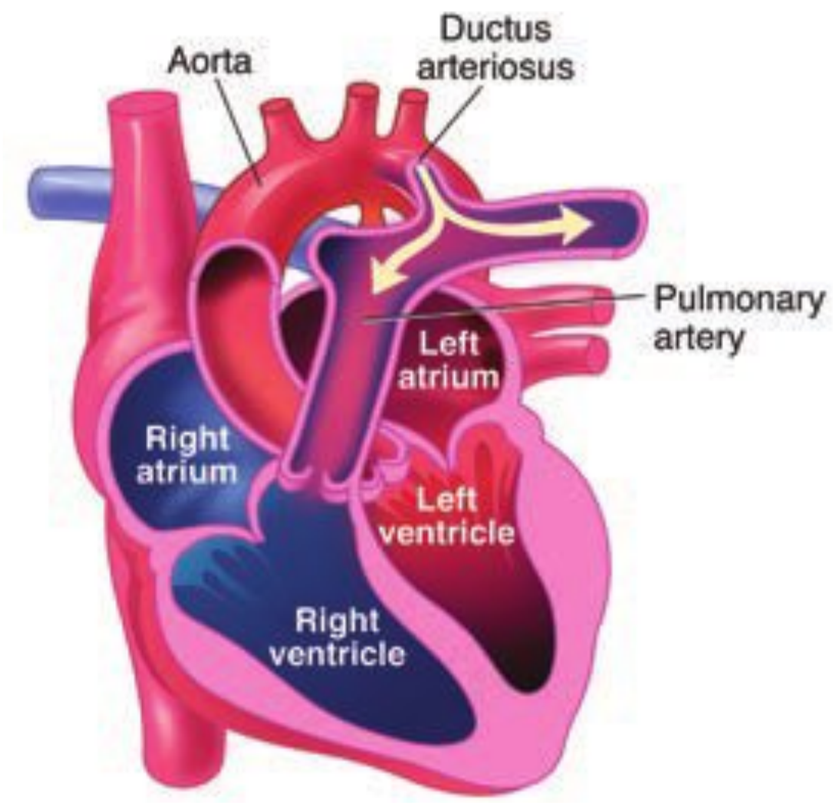


FIGURE 2.13-4. Patent ductus arteriosus with resultant left-to-right shunting. (Reproduced with permission from USMLE-Rx.com.)

Treatment

- Give **indomethacin** (an NSAID) unless the PDA is needed for survival (eg, transposition of the great vessels, tetralogy of Fallot, hypoplastic left heart) or if indomethacin is contraindicated (eg, intraventricular hemorrhage).
- If indomethacin fails or if the child is > 6–8 months of age, surgical closure is required.

KEY FACT

Come **IN** and **CLOSE** the door: give **IN**domethacin to **CLOSE** a PDA.

COARCTATION OF THE AORTA

Constriction of a portion of the aorta, leading to ↑ flow proximal to and ↓ flow distal to the coarctation (Figure 2.13-5). Occurs just distal to the left subclavian artery in 98% of patients. The condition is associated with **Turner** syndrome, berry aneurysms, and male gender. **More than two-thirds of patients have a bicuspid aortic valve.**

KEY FACT

Coarctation of the aorta is associated with Turner syndrome.

History/Pe

- Often presents in childhood with **asymptomatic hypertension (upper extremity hypertension);** the classic physical examination finding is a systolic BP that is **higher in the upper extremities;** the difference in BP between the left and right arm can indicate the point of coarctation.
- A continuous murmur may be heard diffusely across the torso if well-established collaterals are present.
- Lower-extremity claudication, syncope, epistaxis, and headache may be present.
- Additional findings include **weak femoral pulses,** radiofemoral delay, a short systolic murmur in the left axilla, and a forceful apical impulse.
- In infancy, critical coarctation requires a patent PDA for survival. Such infants may present in the first few weeks of life with poor feeding, lethargy, tachypnea, and eventual shocklike state when the PDA closes. Differential cyanosis may be seen with lower O_2 saturation in the left arm and lower extremities (postductal areas) as compared to the right arm (preductal area).

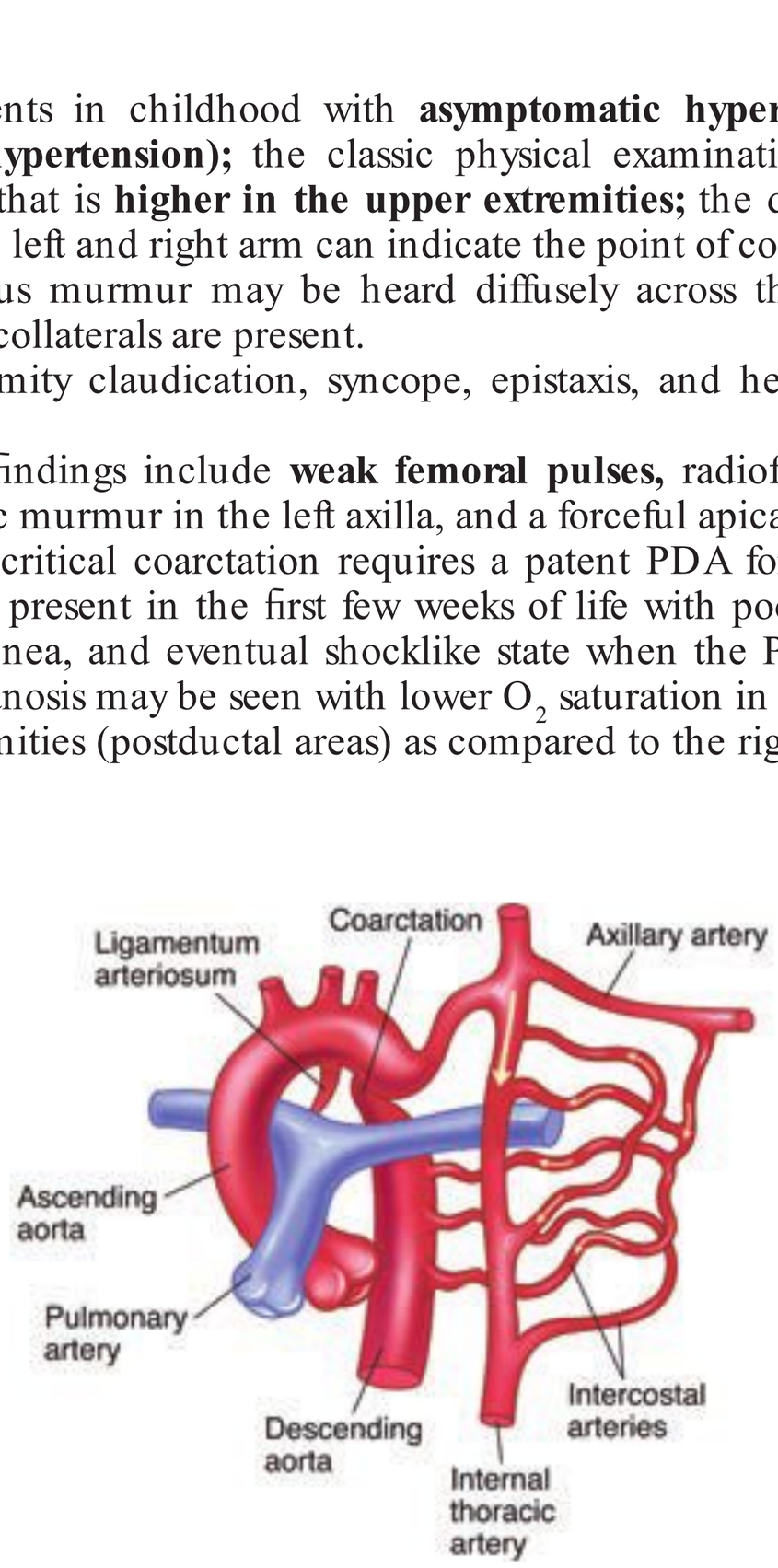


FIGURE 2.13-5. Coarctation of the aorta, causing severe obstruction of flow to the descending thoracic aorta. (Reproduced with permission from USMLE-Rx.com.)

Q

A 2-year-old boy is brought to the pediatrician because of shortness of breath and easy fatigability during play. Examination is notable for tachypnea and a soft holosystolic murmur over the left lower sternal border. What is the most likely cause of the boy's symptoms?

Diagnosis

- **Echocardiography** with color flow Doppler is the diagnostic test of choice.
- CXR in young children may demonstrate cardiomegaly and pulmonary congestion.
- In older children, the following compensatory changes may be seen: LVH on ECG; the **"3" sign on CXR** (see Figure 2.13-6A) due to pre- and post-dilatation of the coarctation segment with aortic wall indentation; and **"rib notching"** (see Figure 2.13-6B) due to collateral circulation through the intercostal arteries.

Treatment

- If severe coarctation presents in infancy, the ductus arteriosus should be kept open with prostaglandin E_1 (PGE_1).
- Surgical correction or balloon angioplasty is controversial.
- Monitor for restenosis, aneurysm development, and aortic dissection.

TRANSPOSITION OF THE GREAT VESSELS

The most common cyanotic congenital heart lesion in the newborn (Figure 2.13-7**).** In this condition, the aorta is connected to the right ventricle and the pulmonary artery to the left ventricle, creating parallel pulmonary and systemic circulations. **Without a septal defect (ASD or VSD) and a PDA, it is incompatible with life.** A PDA alone is usually not sufficient to allow adequate mixing of blood. Risk factors include **diabetic mothers** and, rarely, DiGeorge syndrome.

History/Pe

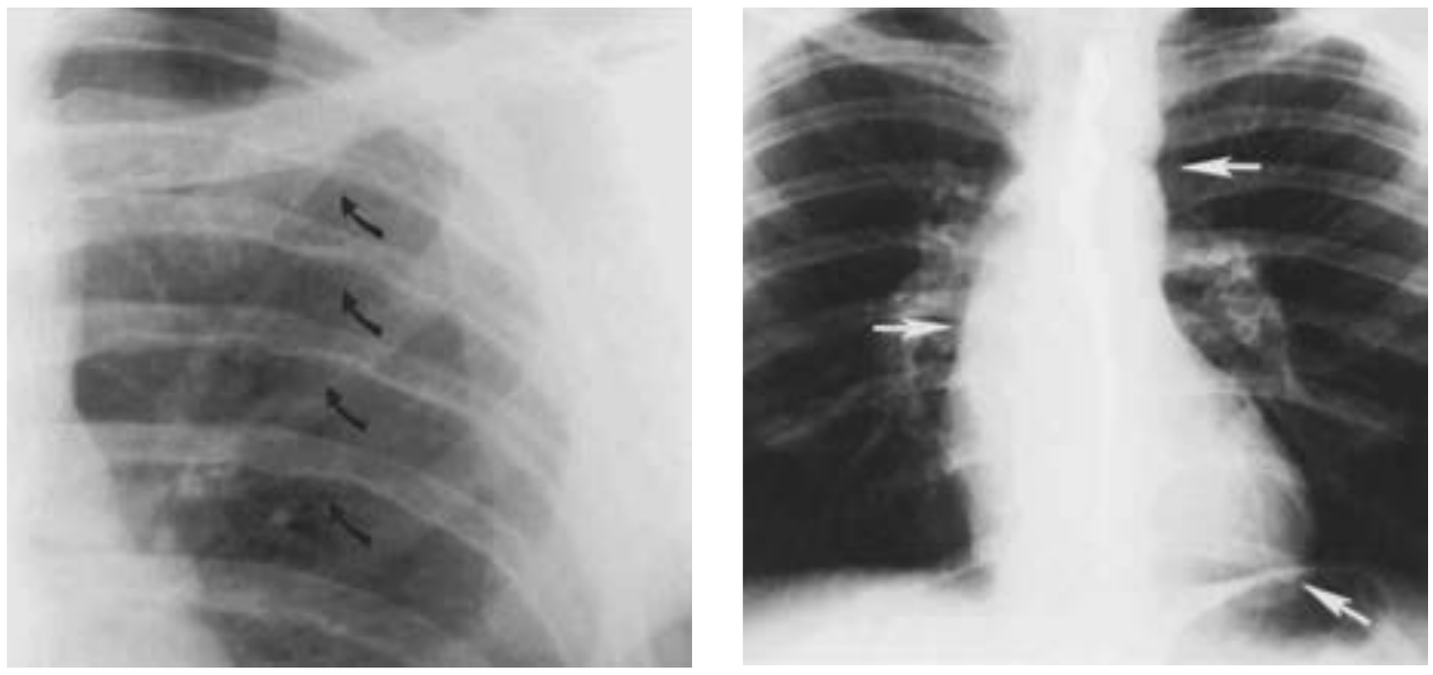
- Critical illness and **cyanosis typically present within first few hours after birth.** Reverse differential cyanosis may be seen if left ventricular outflow tract obstruction (eg, coarctation, aortic stenosis) is also present.
- Examination reveals tachypnea, progressive hypoxemia, and extreme cya-

MNEMONIC

DiGeorge syndrome—

CATCH 22

Cardiac abnormalities (transposition)
Abnormal facies (retrognathia/micrognathia, long face, short philtrum, low-set ears)
Thymic aplasia
Cleft palate
Hypocalcemia (2/2 parathyroid hypoplasia/agenesis)
22q11 deletion



A

B

FIGURE 2.13-6. Coarctation of the aorta. (A) Magnified view of the left upper thorax of a patient with aortic coarctation showing multiple areas of rib notching (arrows). **(B)** PA view of another patient with aortic coarctation showing the "3 sign" of the deformed descending aorta and "E sign" on the barium-filled esophagus. The upper arrow points to the level of coarctation, and the lower arrow marks the apex of the enlarged LV. The arrow on the patient's right indicates the dilated ascending aorta. (Reproduced with permission from Fuster Vet al. Hurst's The Heart, 13th ed. New York, NY: McGraw-Hill; 2011.)

A

This boy probably has a large, untreated ventricular septal defect (VSD) that has led to Eisenmenger syndrome (and right-to-left shunting). There is less turbulence across a large defect (compared with a small one), leading to a softer murmur.

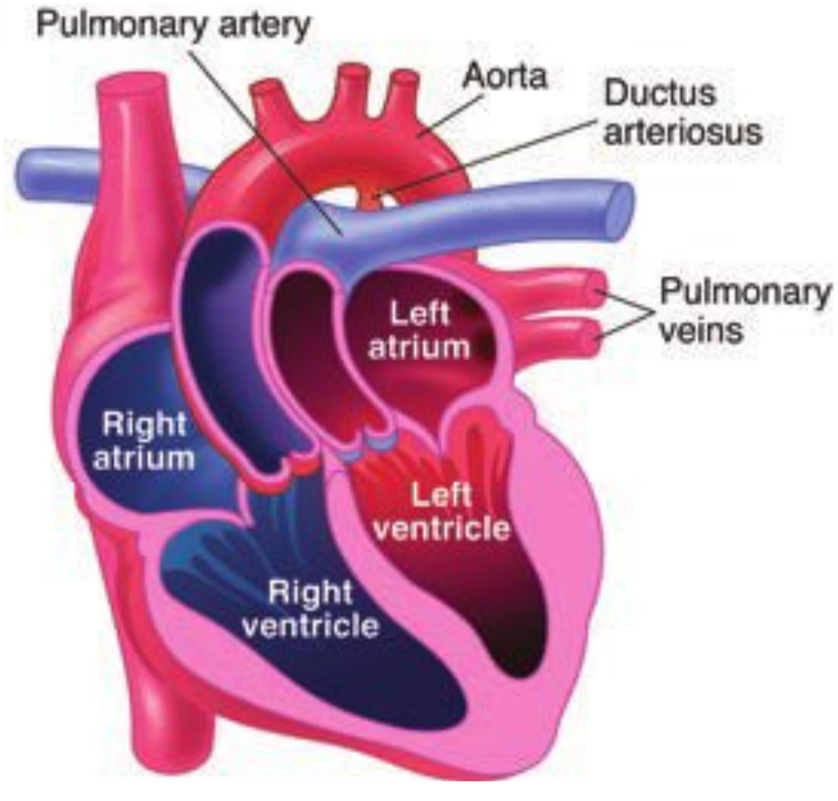


FIGURE 2.13-7. Complete transposition of the great vessels. The right ventricle deoxygenated blood is directed to the aorta and oxygenated blood is directed back to the pulmonary artery. (Reproduced with permission from USMLE-Rx.com.)

nosis. Some patients have signs of CHF, and a single loud S2 is often present. There may not be a murmur if no VSD is present. If a VSD is present, a systolic murmur may be heard at the left sternal border.

Diagnosis

- Echocardiography.
- CXR may show a narrow heart base, absence of the main pulmonary artery segment, an **"egg-shaped silhouette,"** and ↑ pulmonary vascular markings.

Treatment

- Start IV **PGE_1** to maintain or open the PDA.
- If surgery is not feasible within the first few days of life or if the PDA cannot be maintained with prostaglandin, perform **balloon atrial septostomy** to create or enlarge an ASD.
- Surgical correction (arterial or atrial switch) is definitive.

KEY FACT

Transposition of the great vessels is the most common cyanotic heart disease of **newborns.** Tetralogy of Fallot is the most common cyanotic heart disease of **childhood.**

TETRALOGY OF FALLOT

Consists of RV outflow tract obstruction, overriding aorta, RVH, and VSD (Figure 2.13-8). **The most common cyanotic congenital heart disease in children.** Early cyanosis results from right-to-left shunting across the VSD. As right-sided pressures ↓ in the weeks after birth, the shunt direction reverses and cyanosis may ↓. If the degree of pulmonary stenosis is severe, the right-sided pressures may remain high and cyanosis may worsen over time. Risk factors include maternal PKU and DiGeorge syndrome.

History/Pe

- Presents in infancy or early childhood with dyspnea and fatigability. Cyanosis is frequently absent at birth but develops over the first 2 years of life; the degree of cyanosis often reflects the extent of pulmonary stenosis.
- Infants are often asymptomatic until 4–6 months of age, when CHF may develop and manifest as diaphoresis with feeding or tachypnea.

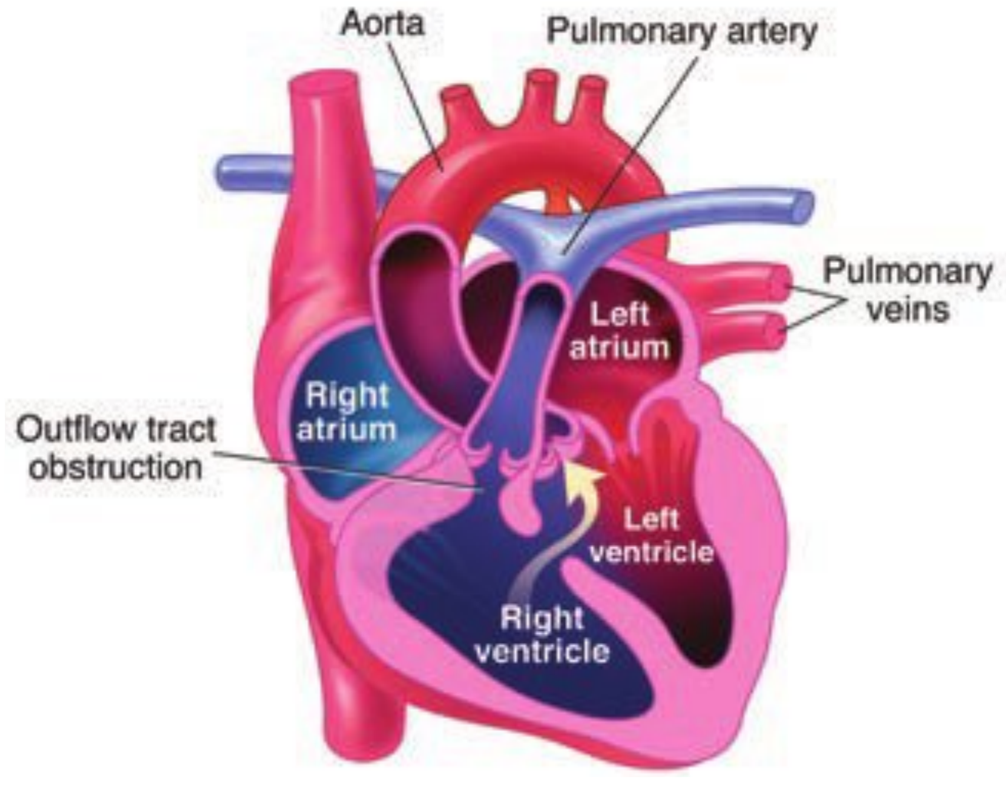


FIGURE 2.13-8. Tetralogy of Fallot. Substantial right ventricular outflow tract obstruction resulting in right-to-left shunting through the ventricular septal defect. (Reproduced with permission from USMLE-Rx.com.)

- **Children often squat** for relief during hypoxemic episodes called **"tet spells,"** which ↑ systemic vascular resistance, thus increasing blood flow to the pulmonary vasculature and improved oxygenation.
- Hypoxemia may lead to FTT or mental status changes.
- Examination reveals a systolic ejection murmur at the left upper sternal border (right ventricular outflow obstruction), a right ventricular heave, and a single S2.

Diagnosis

- Echocardiography and catheterization.
- CXR shows a **"boot-shaped" heart** with ↓ pulmonary vascular markings. Remember that a VSD may result in ↑ pulmonary vascular markings.
- ECG shows right-axis deviation and RVH.

Treatment

- Lesions with severe RV outflow tract obstruction or atresia require immediate PGE_1 to keep the PDA open along with urgent surgical consultation.
- Treat hypercyanotic "tet spells" with O_2, propranolol, phenylephrine, the knee-chest position, fluids, and morphine.
- Temporary palliation can be achieved through the creation of an artificial shunt (eg, balloon atrial septostomy) before definitive surgical correction (Blalock-Taussig shunt).

KEY FACT

Both transposition of the great vessels and tetralogy of Fallot are initially treated with PGE_1 but are definitively treated with surgical correction.

KEY FACT

Signs of autism include no babbling and/or gesturing by 12 months, no two-word phrases by 24 months, impaired social interaction, restricted interests, and insistence on routine.

Child Development

DEVELOPMENTAL MILESTONES

Table 2.13-4 highlights major developmental milestones, with commonly tested milestones highlighted in bold. Table 2.13-5 summarizes critical milestones in language development.

TABLE 2.13-4. Developmental Milestones

Age[a]	Gross Motor	Fine Motor	Language	Social/Cognitive
2 months	**Lifts head/chest when prone.**	Tracks past midline.	Alerts to sound; **coos.**	Recognizes parent; exhibits **social smile.**
4–5 months	**Rolls front to back,** back to front (4 months).	Grasps rattle.	**Laughs and squeals;** orients to voice; begins to make consonant sounds.	Enjoys looking around; laughs.
6 months	**Sits unassisted.**	Transfers objects; demonstrates raking grasp.	**Babbles.**	Demonstrates **stranger anxiety.**
9–10 months	Crawls; cruises; pulls to stand.	Uses **3-finger (immature) pincer grasp.**	Says "mama/dada" (nonspecific); says first word at 11 months.	Waves bye-bye; plays pat-a-cake.
12 months	**Walks alone;** throws object.	Uses **2-finger (mature) pincer grasp.**	Uses **1–3 words.**	Imitates actions; exhibits **separation anxiety.** **Follows 1-step commands.**
2 years	**Walks up/down steps;** jumps.	Builds tower of 6 cubes.	Uses **2-word phrases.**	**Follows 2-step commands;** removes clothes.
3 years	**Rides tricycle;** climbs stairs with alternating feet (3–4 years).	**Copies a circle;** uses utensils.	Uses **3-word sentences.**	Brushes teeth with help; washes/dries hands.
4 years	Hops.	**Copies a cross** (square at 4.5 years).	Knows colors and some numbers.	Exhibits cooperative play; plays board games.
5 years	Skips; walks backward for long distances.	**Copies a triangle;** ties shoelaces; knows left and right; prints letters.	Uses **5-word sentences.**	Exhibits domestic role playing; plays dress-up.

[a]For premature infants < 2 years of age, chronologic age must be adjusted for gestational age. For example, an infant born at 7 months' gestation (2 months early) would be expected to perform at the 4-month level at the chronologic age of 6 months.

TABLE 2.13-5. Major Milestones in Language Development

Age	Milestone
12 months	1 word, 1-step command.
15 months	5 words.
18 months	8 words.
2 years	2-word phrases, 2-step commands. Speech 50% (1/2) intelligible.
3 years	3-word phrases. Speech 75% (3/4) intelligible.
4 years	Speech 100% (4/4) intelligible.

GROWTH

KEY FACT

Newborns can lose up to 10% of their birth weight (BW), but will regain the weight by 2 weeks of life.

KEY FACT

Infants with FTT will first fall off of the **weight** curve, then the **height** curve, and finally the **head circumference** curve.

At each well-child check, height, weight, and head circumference are plotted on growth charts specific for gender and age:

- **Head circumference:** Measured routinely in the first 2 years. ↑ head circumference may indicate hydrocephalus or tumor; ↓ head circumference can point to microcephaly (eg, TORCH infections).
- **Height and weight:** Measured routinely until adulthood. The pattern of growth is more important than the raw numbers. **Infants may lose 5–10% of BW over the first few days but should return to their BW by 14 days.** Infants can be expected to **double their BW by 4–5 months, triple by 1 year, and quadruple by 2 years.**
- **FTT:** Persistent weight less than the fifth percentile for age or "falling off the growth curve" (ie, crossing two major percentile lines on a growth chart). Classified as follows:
  - **Organic:** Due to an underlying medical condition such as cystic fibrosis, congenital heart disease, celiac sprue, pyloric stenosis, chronic infection (eg, HIV), and GERD.
  - **Nonorganic:** Primarily due to psychosocial factors such as poverty, inaccurate mixing of formula (too much water mixed in), maternal depression, neglect, or abuse.
- A careful dietary history and close observation of maternal-infant interactions (especially preparation of formula and feeding) are critical to diagnosis.
- Children should be hospitalized if there is evidence of neglect or severe malnourishment. Calorie counts and supplemental nutrition (if breastfeeding is inadequate) are mainstays of treatment.

SEXUAL DEVELOPMENT

- **Tanner staging:** Performed to assess sexual development in boys and girls (see Figure 2.13-9). Stage 1 is preadolescent; stage 5 is adult. Increasing stages are assigned for testicular and penile growth in boys and breast growth in girls; pubic hair development is used for both stages.
  - **Girls:** The average age of puberty is **10.5 years.** The average age of menarche in US girls is 12.5 years.
  - **Boys:** The average age of puberty is **11.5 years.**

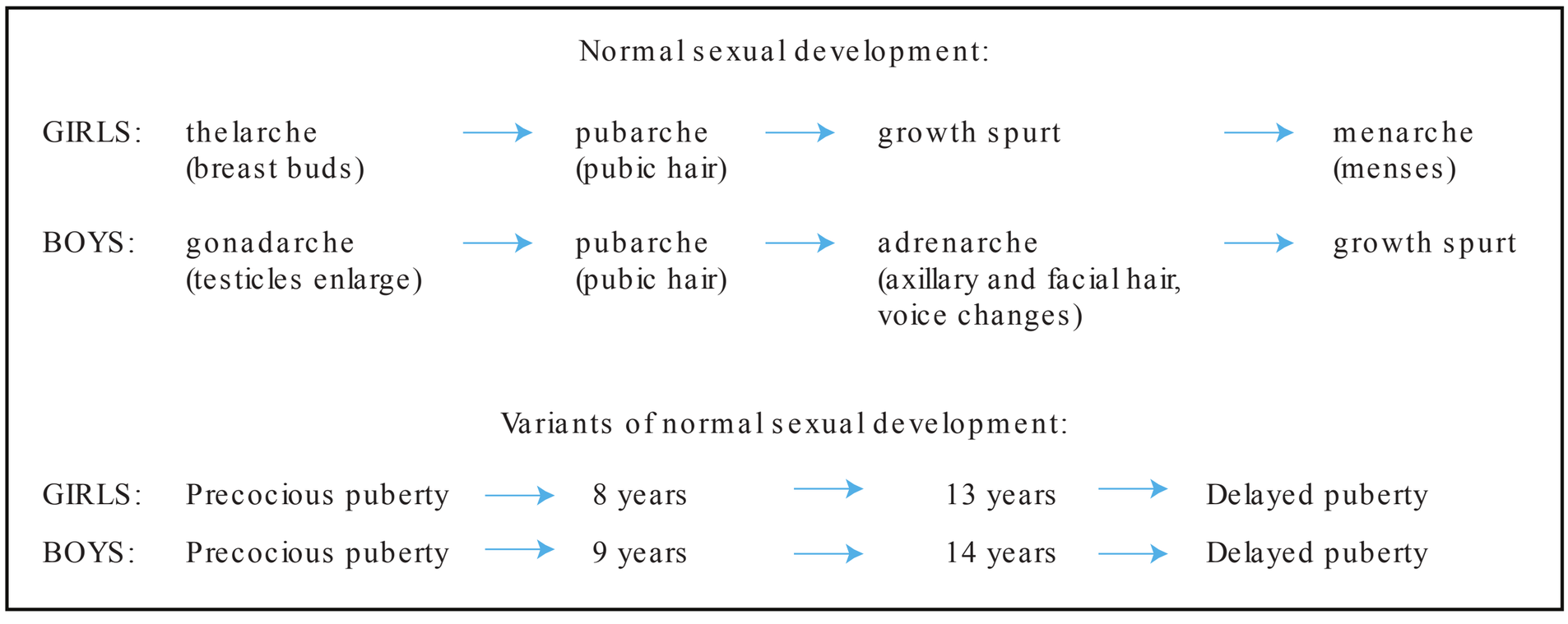


FIGURE 2.13-9. Patterns of sexual development in girls vs boys.

- Variants of normal sexual development are as follows (see also Figure 2.13-9):
  - **Precocious puberty:** Any sign of 2° sexual maturation in girls < 8 years or boys < 9 years of age. Often idiopathic; may be central or peripheral (see the Gynecology chapter).
  - **Delayed puberty:** No testicular enlargement in boys by age 14, or no breast development or pubic hair in girls by age 13.
  - **Constitutional growth delay:** A normal variant, and the most common cause of delayed puberty. The growth curve lags behind others of the same age but remains consistent. There is often a ⊕ family history, and **children ultimately achieve target height potential.**
  - **Pathologic puberty delay:** Rarely, due to systemic disease (eg, IBD), malnutrition (eg, anorexia nervosa), gonadal dysgenesis (eg, Klinefelter syndrome, Turner syndrome), or endocrine abnormalities (eg, hypopituitarism, hypothyroidism, Kallmann syndrome, androgen insensitivity syndrome, Prader-Willi syndrome).

MNEMONIC

Trisomies

21—Age to **D**rink (**D**own syndrome)
18—Age to vote in **E**lections (**E**dwards syndrome)
13—Age of **P**uberty (**P**atau syndrome)

Genetic Disease

Tables 2.13-6–2.13-8 outline common genetic diseases and their associated abnormalities.

TABLE 2.13-6. Trisomies

Disease	Genetic Abnormality	Common Characteristics
Down syndrome	Trisomy 21 as a result of meiotic nondisjunction (95%), Robertsonian translocation (4%), or mosaicism (1%).	The most common chromosomal disorder and cause of intellectual disabilities. Associated with **advanced maternal age.** Presents with intellectual disabilities, flat facial profile, **upslanted eyes** with epicanthal folds, **single palmar crease, general hypotonia,** and extra neck folds (nuchal folds are sometimes seen on prenatal ultrasound). Associated with **atlantoaxial instability, duodenal atresia, Hirschsprung disease,** and **congenital heart disease.** The most common cardiac malformation is AV canal (60%); ASDs, VSDs, and PDAs (20%), and complex congenital heart disease make up the remainder. Also associated with an ↑ risk of **ALL, hypothyroidism,** and **early-onset Alzheimer disease.**
Edwards syndrome	Trisomy 18.	Presents with severe intellectual disabilities, **rocker-bottom feet,** low-set ears, **micrognathia, clenched hands (overlapping fourth and fifth digits),** and a prominent occiput. Associated with congenital heart disease. May have horseshoe kidneys. **Death usually occurs within 1 year of birth.**
Patau syndrome	Trisomy 13.	Presents with severe intellectual disabilities, **microphthalmia, microcephaly,** cleft lip/palate, **holoprosencephaly,** "punched-out" scalp lesions, **polydactyly,** and omphalocele. Associated with congenital heart disease. **Death usually occurs within 1 year of birth.**

TABLE 2.13-7. Sex Chromosome Abnormalities

Disease	Genetic Abnormality	Common Characteristics
Klinefelter syndrome (male)	47,XXY	Characterized by the presence of an inactivated X chromosome (Barr body). Associated with advanced maternal age. One of the most common causes of **hypogonadism** in males. Presents with **testicular atrophy,** a eunuchoid body shape, **tall stature,** long extremities, **gynecomastia,** and **female hair distribution.** Treat with **testosterone** (prevents gynecomastia; improves 2° sexual characteristics).
Turner syndrome (female)	45,XO	Missing 1 X chromosome; no Barr body. Not associated with advanced maternal age. The most common cause of **1° amenorrhea;** due to **ovarian dysgenesis** (treat with estrogen). Features include short stature, shield chest, widely spaced nipples, a **webbed neck, coarctation of the aorta** (↓ femoral pulses), and/or bicuspid aortic valve. May present with **lymphedema of the hands and feet in the neonatal period.** May have horseshoe kidney.
Double Y males	47,XYY	Observed with ↑ frequency among inmates of penal institutions. **Often look normal;** some patients are very tall with severe acne (seen in 1–2% of XYY male patients).

TABLE 2.13-8. Other Genetic Diseases

Disease	Etiology	Mode of Inheritance/Notes
PKU	Caused by ↓ phenylalanine hydroxylase or ↓ tetrahydrobiopterin cofactor. Tyrosine becomes essential, and phenylalanine accumulates and is subsequently converted to its ketone metabolites. Normal at birth; presents within the first few months of life. Presents with intellectual disabilities, **fair hair and skin, eczema, blond hair, blue eyes, and a musty urine odor.** Associated with ↑ risk of heart disease. Modify diet by ↓ **phenylalanine (artificial sweeteners)** and ↑ **tyrosine.** A mother with PKU who wants to become pregnant must restrict her diet as above before conception.	Autosomal recessive PKU is screened for at birth.
Fragile X syndrome	Caused by defect affecting the methylation and expression of the FMR1 gene; a triplet repeat disorder that may show genetic anticipation. Presents with **large jaw, testes, and ears** and with **autistic behaviors.**	**X-linked dominant.** **The second most common genetic cause of intellectual disabilities.**

(continues)

TABLE 2.13-8. Other Genetic Diseases (continued)

Disease	Etiology	Mode of Inheritance/Notes
Fabry disease	Caused by a deficiency of α-galactosidase A that leads to accumulation of ceramide trihexoside in the heart, brain, and kidneys. The first sign is **severe neuropathic limb pain;** also presents with joint swelling. Skin involvement takes the form of **angiokeratomas and telangiectasias.** Findings include **renal failure and an ↑ risk of stroke and MI (thromboembolic events).**	**X-linked recessive.**
Krabbe disease	Absence of galactosylceramide and galactoside (due to galactosylceramidase deficiency), leading to the accumulation of galactocerebroside in the brain. Characterized by **progressive CNS degeneration,** optic atrophy, spasticity, and death within the first 3 years of life.	Autosomal recessive.
Gaucher disease	Caused by a deficiency of **glucocerebrosidase** (also known as acid β-glucosidase) that leads to the accumulation of glucocerebroside in the brain, liver, spleen, and bone marrow. Gaucher cells have a characteristic **"crinkled paper"** appearance with enlarged cytoplasm. May present with **anemia and thrombocytopenia.** The infantile form results in early, rapid neurologic decline. The adult form (more common) is compatible with a **normal life span** and does not affect the brain.	Autosomal recessive.
Niemann-Pick disease	A deficiency of **sphingomyelinase** that leads to the buildup of sphingomyelin cholesterol in reticuloendothelial and parenchymal cells and tissues. Patients with type A die by age 3. May present with a **cherry-red spot and hepatosplenomegaly.**	Autosomal recessive. No man **PICKs (Niemann-PICK)** his nose with his **sphinger.**
Tay-Sachs disease	An absence of hexosaminidase that leads to GM_2 ganglioside accumulation. Infants may appear **normal until 3–6 months of age,** when weakness begins and development slows and regresses. An exaggerated startle response may be seen. Death occurs by age 3. Presents with a **cherry-red spot but no hepatosplenomegaly.** The carrier rate is 1 in 30 Jews of European descent (1 in 300 for others).	Autosomal recessive. **Tay-Sa**X **lacks he**X**osaminidase.**
Metachromatic leukodystrophy	A deficiency of arylsulfatase A that leads to the accumulation of sulfatide in the brain, kidney, liver, and peripheral nerves. **Demyelination leads to progressive ataxia and dementia.**	Autosomal recessive.
Hurler syndrome	A deficiency of α-L-iduronidase. Leads to **corneal clouding, intellectual disabilities, and gargoylism.**	Autosomal recessive.
Hunter syndrome	A deficiency of iduronate sulfatase. A mild form of Hurler syndrome with **no corneal clouding** and mild intellectual disabilities.	**X-linked recessive.** **Hunters** need to **see (no corneal clouding)** to aim for the **X.**

CYSTIC FIBROSIS

An **autosomal recessive** disorder caused by mutations in the CFTR gene (chloride channel) on chromosome 7 and characterized by widespread exocrine gland dysfunction. CF is the most common severe genetic disease in the United States and is most frequently found in **whites.**

History/Pe

- Most patients are diagnosed on newborn screening.
- When patients present with symptoms:
  - Neonates most commonly present with obstruction of the distal ileum due to abnormally thick meconium (15% of presenting cases).
  - Patients < 1 year present with cough, wheezing, or recurrent respiratory infections. They may also have steatorrhea and/or FTT.
  - Most patients > 1 year present with **FTT (due to pancreatic insufficiency)** or **chronic sinopulmonary disease/sputum production.**
- Affected individuals exhibit **recurrent pulmonary infections** (especially with Pseudomonas and Staphylococcus aureus) with subsequent cyanosis, **digital clubbing, chronic cough** (the most common pulmonary symptom), dyspnea, bronchiectasis, hemoptysis, chronic sinusitis, rhonchi, rales, hyperresonance to percussion, and **nasal polyposis.**
- Patients with pancreatic insufficiency usually have **greasy stools** and flatulence; other prominent GI symptoms include pancreatitis, **rectal prolapse,** hypoproteinemia, biliary cirrhosis, jaundice, and esophageal varices.
- Patients who present in late childhood or adulthood are likely to have pancreatic sufficiency; in this case, pulmonary manifestations predominate and the disease tends to have a milder course.
- Additional symptoms include **type 2 DM, "salty-tasting" skin, male infertility** (agenesis of the vas deferens), and **unexplained hyponatremia.**
- Patients are at risk for **fat-soluble vitamin deficiency** (vitamins A, D, E, and K) 2° to malabsorption and may present with manifestations of these deficiencies (ie, night blindness, rickets, neuropathy, coagulopathy).

KEY FACT

Almost all cases of meconium ileus are due to CF.

Diagnosis

- Diagnosed by a **sweat chloride test** (pilocarpine electrophoresis).
- Confirmed by genetic testing.
- Most states now perform **mandatory newborn screening.**

Treatment

- Pulmonary manifestations are managed with chest physical therapy, bronchodilators, corticosteroids, antibiotics **(should cover** Pseudomonas**),** and DNase.
- Administer **pancreatic enzymes and fat-soluble vitamins** A, D, E, and K for malabsorption.
- Nutritional counseling and support with a **high-calorie and high-protein diet** are essential for health maintenance.
- Patients who have severe disease but can tolerate surgery may be candidates for lung or pancreas transplants. Life expectancy was once ~ 20 years, but with newer treatments it is increasing to past age 40.

Pediatric Gastroenterological Disease

INTUSSUSCEPTION

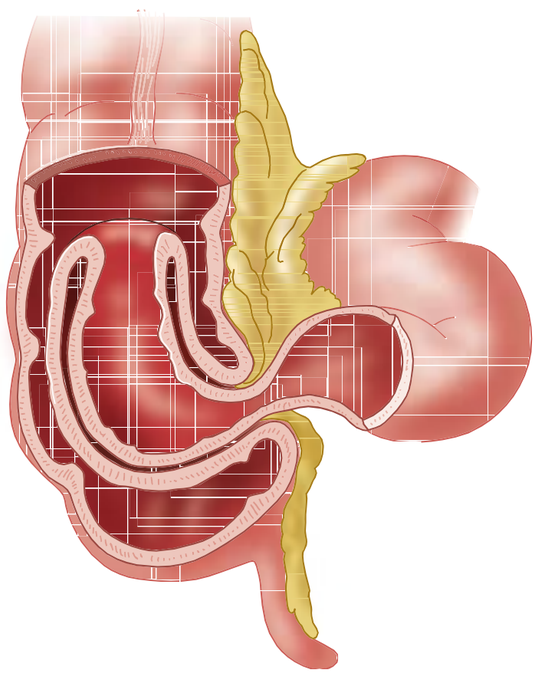
A condition in which a portion of the bowel invaginates or "telescopes" into an adjacent segment, usually proximal to the ileocecal valve (see Figure 2.13-10A). **The most common cause of bowel obstruction in children between the ages of 6 months and 3 years (boys > girls).** Etiology is unclear in most children. Risk factors include **conditions with potential lead points,** including **Meckel diverticulum,** intestinal lymphoma (> 6 years of age), submucosal hematoma (as in Henoch-Schönlein purpura), polyps, and CF (lead point is inspissated stool). Antecedent GI or URI is seen in many children, which may cause formation of a lead point through enlargement of Peyer patches.

History/Presentation

- Presents with abrupt-onset, **episodic abdominal pain** in apparently healthy children, often accompanied by flexed knees and vomiting. The child may appear well between episodes if intussusception is released.
- The classic triad is **severe abdominal pain, vomiting (initially nonbilious, then bilious as obstruction develops), and bloody mucus in stool ("currant jelly stool,"** a late finding).
- On examination, look for abdominal tenderness, a ⊕ stool guaiac, a palpable **"sausage-shaped" RUQ abdominal mass,** and "empty" RLQ on palpation (Dance sign).

Diagnosis/Treatment

- **Ultrasonography** is the test of choice and may show a **"target sign"** (see Figure 2.13-10B); ultrasound must be carried out **during a painful episode** in order to diagnose intussusception.
- **Abdominal plain films** are often normal early in the disease, but later they may show small bowel obstruction, perforation, or a soft tissue mass.



A



B

FIGURE 2.13-10. Intussusception. (A) Ileocolic intussusception, the most common location in children. **(B)** Transabdominal ultrasound shows the classic "target sign" of intussusception in cross-section. (Part A reproduced with permission from Doherty GM. Current Diagnosis & Treatment: Surgery, 13th ed. New York, NY: McGraw-Hill; 2010. Part B reproduced with permission from Ma OJ et al. Emergency Ultrasound, 2nd ed. New York, NY: McGraw-Hill; 2008.)

KEY FACT

The classic triad of abdominal pain, vomiting, and currant jelly stool only occurs in one-third of patients.

Q

A 3-day-old boy born at 39 weeks gestational age via normal spontaneous vaginal delivery has failed to pass meconium and today displays abdominal distention and five episodes of nonbilious vomiting. Rectal exam shows no stool in the rectal vault. Air contrast enema shows an obstruction at the ileum. What is the most likely cause of this patient's symptoms?

KEY FACT

Air insufflation enema is preferred over water or barium-contrast enema for diagnosis and management of intussusception, as it is faster and carries a lower risk of complications.

- Correct any volume or electrolyte abnormalities, check CBC for leukocytosis, and consider an NG tube for decompression.
- In the setting of high clinical suspicion, an **air insufflation enema** should be performed without delay, as it is diagnostic and curative in the vast majority of patients.
- Surgical resection is indicated if the child has peritoneal signs, enema reduction is unsuccessful, or a pathologic lead point is identified.

PYLORIC STENOSIS

Hypertrophy of the pyloric sphincter, leading to gastric outlet obstruction. More common in **firstborn infant boys;** associated with tracheoesophageal fistula, formula feeding, and **maternal erythromycin** ingestion.

History/Pe

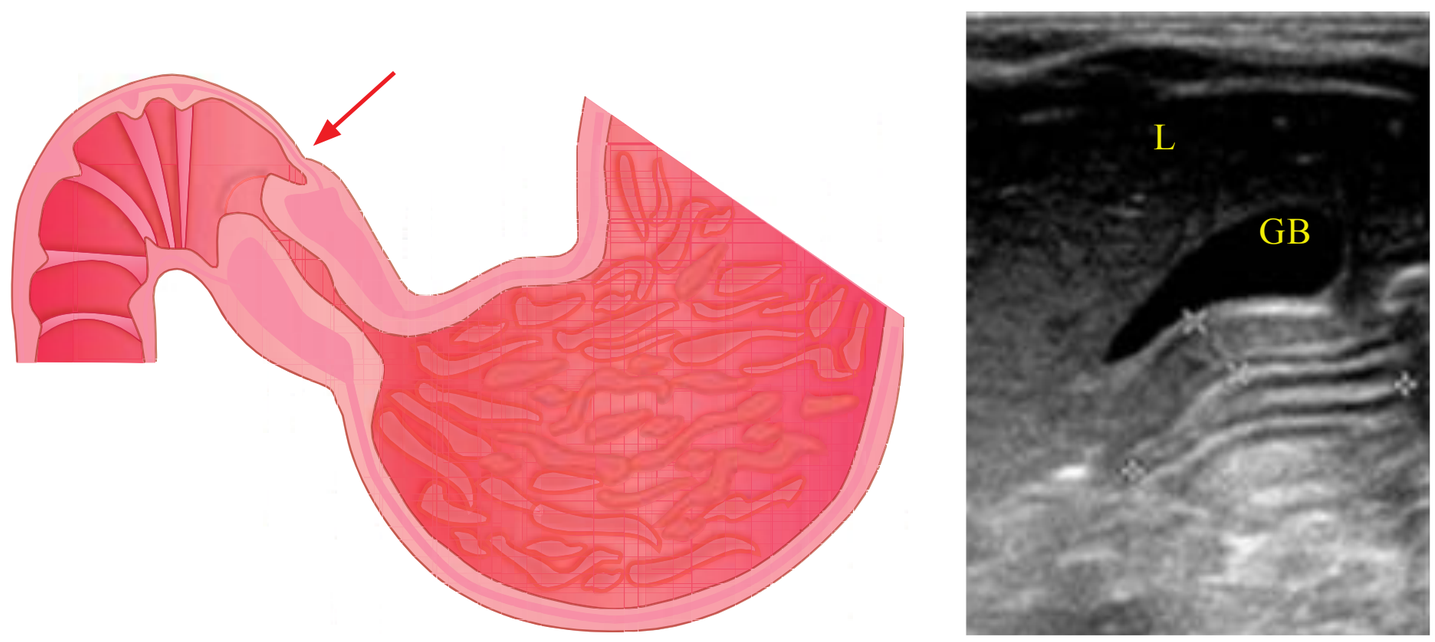
- **Nonbilious emesis** typically begins around **3–5 weeks of age** and progresses to **projectile emesis** after most or all feedings.
- Infants are generally hungry after episodes of vomiting; they initially feed well but eventually suffer from dehydration and malnutrition.
- Examination may reveal a **palpable olive-shaped,** mobile, nontender epigastric mass and visible gastric peristaltic waves.

KEY FACT

Pyloric stenosis is the most common cause of GI tract obstruction in infancy; nearly all cases are diagnosed between 3 and 12 weeks of age.

Diagnosis

- **Abdominal ultrasound** is the imaging modality of choice and reveals a thickened, elongated pylorus (see Figure 2.13-11).
- **Laboratory workup reveals hypochloremic, hypokalemic metabolic alkalosis; emesis results in loss of HCl and renin-angiotensin-aldosterone axis activation.**
- Barium studies show a narrow pyloric channel ("string sign") or a pyloric beak.



A B

FIGURE 2.13-11. Hypertrophic pyloric stenosis. (A) Schematic representation of a hypertrophied pylorus. The arrow denotes protrusion of the pylorus into the duodenum. **(B)** Longitudinal ultrasound of the pylorus showing a thickened pyloric musculature (X's) over a long pyloric channel length (plus signs). L = liver; GB = gallbladder. (Part A adapted with permission from Doherty GM. Current Diagnosis & Treatment: Surgery, 13th ed. New York, NY: McGraw-Hill; 2010. Part B reproduced with permission from USMLE-Rx.com.)

A

This infant most likely has meconium ileus resulting from cystic fibrosis (CF); however, Hirschsprung disease should remain on the differential diagnosis, as it also can cause delayed meconium passage. Meconium ileus causes obstruction at the level of the ileum, whereas Hirschsprung disease causes rectosigmoid obstruction and rectal exam may result in the expulsion of stool.

Treatment

- Make NPO, establish IV access, and correct dehydration and acid-base/electrolyte abnormalities.
- Surgical correction with **pyloromyotomy is definitive treatment.**

MECKEL DIVERTICULUM

Caused by failure of the omphalomesenteric (or vitelline) duct to obliterate, resulting in the formation of a **true diverticulum** (containing all three layers of the small intestine). The heterotopic gastric tissue present in most Meckel diverticula causes intestinal ulceration and painless hematochezia. This is the most common congenital abnormality of the small intestine, affecting up to 2% of children (boys > girls). Most frequently symptomatic in **children < 2 years of age.**

History/Pe

- Typically asymptomatic, and often discovered incidentally.
- Classically presents with **painless rectal bleeding.**
- Complications include intestinal perforation or obstruction, diverticulitis (which can mimic acute appendicitis), and intussusception.

Diagnosis

- A **Meckel scintigraphy scan** (technetium-99m pertechnetate; detects ectopic gastric tissue) is diagnostic.
- Plain films have limited value but can be useful in diagnosing obstruction or perforation.

Treatment

Treatment is **surgical excision** of the diverticulum together with the adjacent ileal segment, which may be ulcerated. Indications for urgent/emergent surgery include hemorrhage, diverticulitis, intestinal perforation, and obstruction/intussusception.

HIRSCHSPRUNG DISEASE

Congenital lack of ganglion cells in the distal colon, leading to decreased motility due to unopposed smooth muscle tone in the absence of enteric relaxing reflexes and uncoordinated peristalsis (Figure 2.13-12). Associated with male gender, **Down syndrome,** Waardenburg syndrome, and multiple endocrine neoplasia type 2.

History/Pe

- Neonates present with **failure to pass meconium within 48 hours of birth,** accompanied by bilious vomiting and FTT; children with less severe lesions may present later in life with chronic constipation.
- Physical examination may reveal abdominal distention and **explosive discharge of stool following a rectal examination;** lack of stool in the rectum; or abnormal sphincter tone.

Diagnosis

- **Barium enema** is the imaging study of choice and reveals a narrowed distal colon with proximal dilation. Plain films reveal distended bowel loops with a paucity of air in the rectum.

MNEMONIC

Meckel rule of 2's—

Occurs in **2%** of the population.
2% symptomatic by age **2.**
2 times more common in boys.
Contains **2** types of tissue (gastric and pancreatic).
2 inches long.
Found within **2** feet of the ileocecal valve.

KEY FACT

Bleeding is the most common complication of Meckel diverticulum; it may be minimal, or severe enough to cause hemorrhagic shock.



FIGURE 2.13-12. Hirschsprung disease. Retrograde barium enema shows small caliber of the left colon and rectum in comparison to the more dilated transverse colon. Filling defects in the descending/sigmoid colon represent feces. (Reproduced with permission from USMLE-Rx.com.)

Q

A 3-week-old ex-term infant boy is brought to the ED after experiencing vomiting of increasing frequency and intensity for the past week. His parents state that he now vomits forcefully after every meal and enthusiastically attempts to eat immediately after vomiting. The infant appears lethargic, with sunken fontanelles and decreased skin turgor. The abdomen is soft, nontender, and nondistended; no masses are felt. What is the most likely cause of this infant's symptoms?

- Anorectal manometry detects failure of the internal sphincter to relax after distention of the rectal lumen. It is typically used in atypical presentations or older children.
- **Rectal biopsy** confirms the diagnosis and reveals absence of the myenteric (Auerbach) plexus and submucosal (Meissner) plexus along with hypertrophied nerve trunks enhanced with acetylcholinesterase stain.

KEY FACT

The definitive diagnosis of Hirschsprung disease requires a rectal biopsy.

Treatment

Traditionally a **two-stage surgical repair** is used involving the creation of a diverting colostomy at the time of diagnosis, followed several weeks later by a **definitive "pull-through" procedure** connecting the remaining colon to the rectum.

MALROTATION WITH VOLVULUS

Congenital malrotation of the midgut results in abnormal positioning of the small intestine (cecum in the right hypochondrium) and formation of fibrous bands (Ladd bands), which predispose to obstruction and constriction of blood flow.

History/Pe

- Often presents in the **first month of life** with **bilious emesis,** crampy abdominal pain, distention, and passage of blood or mucus in the stool.
- Postsurgical adhesions can lead to obstruction and volvulus at any point in life.

Diagnosis

- AXR may reveal the characteristic **"bird-beak" appearance** and air-fluid levels but may also appear normal.
- **Upper GI series** is the study of choice if the patient is stable and shows an abnormal location of the ligament of Treitz. Ultrasound may be used, but its sensitivity is contingent on the experience of the ultrasonographer.

Treatment

- NG tube insertion to decompress the intestine; IV fluid hydration.
- Emergent surgical repair when volvulus is gastric; surgery or endoscopy when volvulus is intestinal.

A

This infant is most likely suffering from pyloric stenosis, an obstruction of the gastric outlet secondary to hypertrophy and hyperplasia of the muscular layers of the pylorus. Note that most (60–80%) but not all infants present with an olive-shaped abdominal mass.

NECROTIZING ENTEROCOLITIS

A condition in which a portion of the bowel (most commonly the terminal ileum/proximal colon) undergoes necrosis. The **most common GI emergency in neonates;** most frequently seen in **premature infants** but can occur in full-term infants as well. Risk factors include low birth weight, hypotension, and enteral feeding (especially formula).

History/Pe

- Symptoms usually present within the **first few days or weeks of life** and are nonspecific, including feeding intolerance, delayed gastric emptying, abdominal distention, and bloody stools.
- Symptoms can rapidly progress to intestinal perforation, peritonitis, abdominal erythema, and shock. Maintain a high index of suspicion.

Diagnosis

- Lab findings are nonspecific and may show hyponatremia, metabolic acidosis, leukopenia or leukocytosis with left shift, thrombocytopenia, and coagulopathy (DIC with prolonged PT/aPTT and a ⊕ D-dimer).
- **Plain abdominal radiographs** are the imaging modality of choice and may show dilated bowel loops, **pneumatosis intestinalis** (intramural air bubbles representing gas produced by bacteria within the bowel wall; see Figure 2.13-13), portal venous gas, or abdominal free air (in the case of bowel perforation). Serial abdominal plain films should be taken every 6 hours.
- Ultrasound may also be helpful in discerning free air, areas of loculation, and bowel necrosis.

KEY FACT

Pneumatosis intestinalis on plain films is pathognomonic for NEC in neonates.

Treatment

- Initiate supportive measures, including NPO, an orogastric tube for gastric decompression, correction of dehydration and electrolyte abnormalities, TPN, and IV antibiotics.
- **Indications for surgery are perforation (free air under the diaphragm) or worsening radiographic signs** on serial abdominal plain films. An ileostomy with mucous fistula is typically performed, with a reanastomosis later.
- Complications include formation of intestinal **strictures** and **short-bowel syndrome.**

Pediatric Immune-Mediated Disease

IMMUNODEFICIENCY DISORDERS

Congenital immunodeficiencies are rare and often present with chronic or recurrent infections (eg, chronic thrush), unusual or opportunistic organisms, incomplete treatment response, or FTT. Categorization is based on the single immune system component that is abnormal (see also Table 2.13-9).

KEY FACT

Flashback to immunology:

- **B cells:** Make **immunoglobulins** and are responsible for immunity against **extracellular bacteria.**
- **T cells:** Responsible for immunity against **intracellular bacteria, viruses, and fungi.**

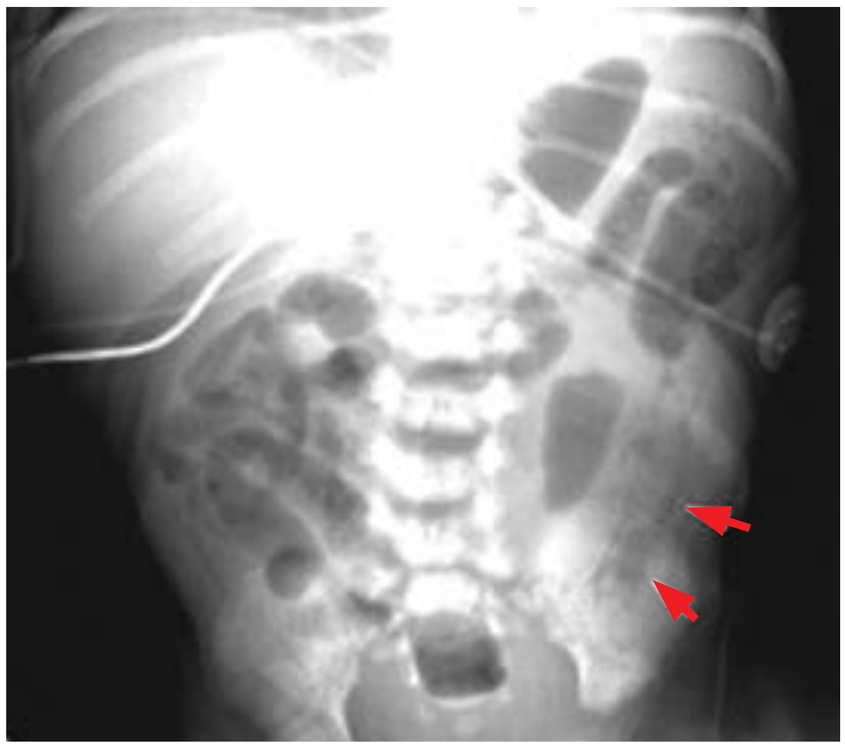


FIGURE 2.13-13. Pneumatosis intestinalis. Short arrows highlight pneumatosis intestinalis on an AXR of a patient with necrotizing enterocolitis. (Reproduced with permission from Brunicardi FC et al. Schwartz's Principles of Surgery, 9th ed. New York, NY: McGraw-Hill; 2010.)

TABLE 2.13-9. Pediatric B-Cell and T-Cell Deficiencie

Disorder	Description	Infection risk/type	Diagnosis/treatment
		B-cell disorders	
Bruton agammaglobulinemia	An **X-linked recessive B-cell** deficiency found only in **boys.** Symptoms begin **after 6 months of age,** when maternal IgG (transferred transplacentally) is no longer active.	Life-threatening; characterized by encapsulated Pseudomonas, S pneumoniae, and Haemophilus infections after 6 months of age.	Quantitative Ig levels. If low, confirm with B- and T-cell subsets (B cells are absent; T cells are often high). **Absent tonsils and other lymphoid tissue** may provide a clue. Treat with prophylactic antibiotics and **IVIG.**
Common variable immunodeficiency (CVID)	Usually a combined B- and T-cell defect. **All Ig levels are low** (in the 20s and 30s). **Normal B-cell numbers; ↓ plasma cells.** Symptoms usually present later in life (15–35 years of age).	↑ pyogenic upper and lower respiratory infections. ↑ risk of lymphoma and autoimmune disease.	Quantitative Ig levels; confirm with B- and T-cell subsets. **Treat with IVIG.**
IgA deficiency	Mild; **the most common immunodeficiency.** **↓ IgA levels only.**	Usually asymptomatic; patients may develop recurrent respiratory or GI infections (Giardia). **Anaphylactic transfusion reaction** due to anti-IgA antibodies is a common presentation.	Quantitative IgA levels; treat infections. **Be careful giving IVIG,** as it can lead to the production of anti-IgA antibodies and cause severe allergic reactions. If IVIG is necessary, give IgA-depleted IVIG.
		T-cell disorders	
Thymic aplasia (DiGeorge syndrome)	See the mnemonic **CATCH 22.** Presents with **tetany** (2° to **hypocalcemia**) in the first days of life. Autosomal dominant.	Variable risk of infection. ↑↑↑ infections with **viruses, fungi, and PCP pneumonia.** X-ray film may show **absent thymic shadow.**	Absolute T-lymphocyte count; mitogen stimulation response; delayed hypersensitivity skin testing. Treat with bone marrow transplantation and IVIG for antibody deficiency; give PCP prophylaxis. Thymus transplantation is an alternative.
		Combined disorders	
Ataxia-telangiectasia	Progressive **cerebellar ataxia and oculocutaneous telangiectasias.** Caused by an autosomal recessive mutation in gene responsible for repair of dsDNA breaks.	↑ **incidence of malignancies,** including non-Hodgkin lymphoma, leukemia, and gastric carcinoma.	No specific treatment; may require IVIG depending on the severity of the Ig deficiency.

(continues)

TABLE 2.13-9. Pediatric B-Cell and T-Cell Deficiencie (continued)

Disorder	Description	Infection risk/type	Diagnosis/treatment
		Combined disorders	
SCID	Most commonly X-linked recessive. Severe lack of B and T cells due to a defect in stem cell maturation and ↓ adenosine deaminase. Referred to as "bubble boy disease," because children are confined to an isolated, sterile environment.	Severe, frequent bacterial infections; chronic candidiasis; opportunistic organisms.	Treat with bone marrow or stem cell transplantation and IVIG for antibody deficiency. **Requires PCP prophylaxis.**
Wiskott-Aldrich syndrome	An **X-linked recessive** disorder seen **only in male patients.** Symptoms usually present at birth. Patients have ↑ IgE/IgA, ↓ **IgM,** and **thrombocytopenia.** The classic presentation involves **bleeding, eczema, and recurrent otitis media.** Remember the mnemonic **WIPE:** **W**iskott-Aldrich **I**nfections **P**urpura (thrombocytopenic) **E**czema.	↑↑ risk of atopic disorders, lymphoma/leukemia, and infection from S pneumoniae, S aureus, and H influenzae type b (**encapsulated organisms;** think back to how IgM functions).	Treatment is supportive (IVIG and antibiotics). **Patients rarely survive to adulthood.** Patients with severe infections may be treated with bone marrow transplantation.

- **B-cell deficiencies:** Most common (50%). Typically present **after 6 months of age** with recurrent sinopulmonary, GI, and urinary tract infections with **encapsulated organisms** (Haemophilus in*fl*uenzae, Streptococcus pneumoniae, Neisseria meningitidis). **Treat with IVIG (except for IgA deficiencies).**
  - Bruton agammaglobulinemia can be confused with transient hypogammaglobulinemia of infancy (THI), as both are characterized by ↑ susceptibility to infections at ~ 6 months of age, when transplacental maternal IgG is no longer active. B cells are ↓ in Bruton, whereas those in THI are normal.
  - Bruton agammaglobulinemia and common variable immunodeficiency (CVID) also have similar symptoms, but the former is found in boys ~ 6 months of age, whereas CVID is seen in older men and women (15–35 years of age), and its symptoms are less severe.
- **T-cell deficiencies:** Tend to present earlier (1–3 months) with **opportunistic and low-grade fungal, viral, and intracellular bacterial infections** (eg, mycobacteria). 2° B-cell dysfunction can also be seen.
- **Phagocyte deficiencies:** Characterized by mucous membrane infections, abscesses, and poor wound healing. **Infections with catalase-⊕ organisms** (eg, S aureus), **fungi, and gram-⊖ enteric organisms are common. See** Table 2.13-10**.**
- **Complement deficiencies:** Present in children with **congenital asplenia or splenic dysfunction (sickle cell disease).** Characterized by recurrent **bacterial** infections with **encapsulated organisms.** See Table 2.13-11**.**

Q

A newborn presents with lymphedema of the hands and feet, ↓ femoral pulses, a webbed neck, widely spaced nipples, short fourth metacarpals, and nail dysplasia. What form of hormone replacement therapy will the child need in the future?

TABLE 2.13-10. Pediatric Phagocytic Deficiencie

disorder	description	infection risk/type	diagnosis/treatment
Chronic granulomatous disease (CGD)	An X-linked (2/3) or autosomal-recessive (1/3) disease with deficie t superoxide production by PMNs and macrophages. Anemia, lymphadenopathy, and hypergammaglobulinemia may be present.	Chronic skin, lymph node, pulmonary, GI, and urinary tract infections; osteomyelitis and hepatitis. **Infecting organisms are catalase** ⊕ (Saureus, Escherichia coli, Candida, Klebsiella, Pseudomonas, Aspergillus). May have granulomas of the skin and GI/GU tracts.	Absolute neutrophil count with neutrophil assays. The dihydrorhodamine **(DHR) test is diagnostic for CGD; nitroblue tetrazolium test is the old gold standard.** **Treat with daily TMP-SMX;** make judicious use of antibiotics during infections. IFN-γ can ↓ the incidence of serious infection. BMT and gene therapy are new therapies.
Leukocyte adhesion deficien y	A defect in the chemotaxis of leukocytes. ↓ phagocytic activity.	Recurrent skin, mucosal, and pulmonary infections. May present as **omphalitis in the newborn** period with **delayed separation of the umbilical cord (> 14 days postbirth).**	**No pus with minimal inflamm tion in wounds** (due to a chemotaxis defect). High WBCs in blood. BMT is curative.
Chédiak-Higashi syndrome	An autosomal recessive disorder that leads to a defect in neutrophil chemotaxis/ microtubule polymerization. The syndrome includes **partial oculocutaneous albinism, peripheral neuropathy, and neutropenia.**	↑↑ incidence of overwhelming pyogenic infections with Streptococcus pyogenes, Saureus, and Pseudomonas species.	Look for giant granules in neutrophils. BMT is the treatment of choice.
Job syndrome (Hyperimmunoglobulin Esyndrome)	A defect in neutrophil chemotaxis. Remember the mnemonic **FATED:** Coarse **F**acies **A**bscesses (Saureus) Retained primary **T**eeth Hyper-Ig**E** (eosinophilia) **D**ermatologic (severe eczema)	Recurrent Saureus infections and abscesses.	Treat with penicillinase-resistant antibiotics and IVIG.

A

Estrogen replacement therapy is required for ovarian dysgenesis. Without exogenous estrogen, this child will be at ↑ risk of delayed puberty and osteoporosis later in life.

KAWASAKI DISEASE

A multisystemic acute vasculitis that primarily affects young children (80% are < 5 years of age), particularly those of **Asian ancestry.** Divided into acute, subacute, and chronic phases.

Diagnosis

- **Acute phase:** 1–2 weeks from onset (see Table 2.13-12 for diagnostic criteria).

TABLE 2.13-11. Pediatric Complement Disorders

Disorder	Description	Infection risk/type	Diagnosis/treatment
C1 esterase inhibitor deficiency (hereditary angioedema)	An autosomal dominant disorder with **recurrent episodes of angioedema** lasting 2–72 hours and provoked by stress or trauma.	Can lead to life-threatening airway edema.	Total hemolytic complement (CH50) to assess the quantity and function of complement. Purified C1 esterase and FFP can be used prior to surgery.
Terminal complement deficiency (C5–C9)	Inability to form MAC.	**Recurrent** Neisseria **infections, meningococcal or gonococcal.** Rarely, lupus or glomerulonephritis.	Meningococcal vaccine and appropriate antibiotics.

- **Subacute phase:** 2–8 weeks from onset. Manifestations are thrombocytosis and elevated ESR. Untreated children may begin to develop **coronary artery aneurysms** (40%); all patients should be assessed by **echocardiography** at diagnosis.
- **Chronic phase: > 8 weeks from onset;** begins when all clinical symptoms have disappeared, and lasts until ESR returns to baseline. **Untreated children are at risk of aneurysmal expansion and MI.**

Diagnosis

- Laboratory workup:
  - **Acute phase:** Normochromic anemia, leukocytosis with left shift, high ESR and CRP.
  - **Subacute phase:** Thrombocytosis. ESR and CRP gradually decrease during this phase.
- **Echocardiogram** at time of diagnosis to establish a baseline for longitudinal follow-up of coronary artery morphology. Follow-up for uncomplicated cases usually at 2 weeks and 6–8 weeks after diagnosis.

Treatment

- High-dose **ASA** (for antiinflammatory, antipyretic, and antithrombotic effects) and **IVIG** (to prevent coronary artery aneurysms).

TABLE 2.13-12. Clinical Manifestations of Kawasaki Disease

5 days of fever and at least 4 of the following 5 criteria:

1. Bilateral, nonexudative, painless conjunctivitis sparing the limbic area.
2. Oral mucosal changes: erythematous mouth/pharynx, "strawberry tongue" (Figure 2.13-14), or cracked lips.
3. Rash: primarily truncal, polymorphous, erythematous.
4. Peripheral extremity changes: induration of hands and feet, erythematous and desquamating palms and soles.
5. Cervical lymphadenopathy (> 1.5 cm): generally painful and unilateral.

Other manifestations (not required for diagnosis) include sterile pyuria, gallbladder hydrops, hepatitis, arthritis.

Adapted with permission from the Centers for Disease Control and Prevention. http://www.cdc.gov/kawasaki/. Accessed 5/29/2015.

KEY FACT

Untreated Kawasaki disease can lead to coronary aneurysms in up to 25% of patients.



FIGURE 2.13-14. Kawasaki disease. Strawberry tongue and bright red, swollen lips. (Reproduced with permission of Dong Soo Kim/Wikimedia Commons.)

MNEMONIC

Kawasaki disease symptoms—

CRASH and BURN

Conjunctivitis
Rash
Adenopathy (unilateral)
Strawberry tongue
Hands and feet (red, swollen, fla y skin)
BURN [fever > 40°C (> 104°F) for ≥ 5 days]

KEY FACT

Kawasaki disease and scarlet fever may both present with "strawberry tongue," rash, desquamation of the hands and feet, and erythema of the mucous membranes. However, children with scarlet fever have normal lips and no conjunctivitis.

- Low-dose ASA is then continued, usually for 6 weeks. Children who develop coronary aneurysms may require chronic anticoagulation with ASA or other antiplatelet medications. Patients taking ASA are at risk of developing Reye syndrome.
- Corticosteroids may be used in IVIG-refractory cases, but **routine use is not recommended.**

JUVENILE IDIOPATHIC ARTHRITIS

An autoimmune disorder manifesting as arthritis with **"morning stiffness"** and gradual loss of motion that is present for at least 6 weeks in a patient < **16 years of age.** Formerly known as juvenile rheumatoid arthritis (JRA). Approximately 95% of cases resolve by puberty. More common in girls than in boys. The subtypes of JIA are described in Table 2.13-13.

Diagnosis

See Table 2.13-13.

Treatment

- **NSAIDs** and strengthening exercises.
- Corticosteroids (for carditis) and immunosuppressive medications (methotrexate, anti–tumor necrosis factor agents such as etanercept) are second-line agents.

Pediatric Infectious Disease

ACUTE OTITIS MEDIA

A suppurative infection of the middle ear cavity that is common in children. Up to 75% of children have at least 3 episodes by age 2. Common pathogens include S pneumoniae, **nontypeable** H in*fl*uenzae, M catarrhalis, and viruses such as influenza A, RSV, and parainfluenza virus.

TABLE 2.13-13. Juvenile Idiopathic Arthritis Subtypes

Subtype	Presentation	RF and ANA Status	Notes
Pauciarticular (oligoarthritis)	Involves 4 or fewer joints (usually weight-bearing); no systemic symptoms. Uveitis is common; requires slit-lamp exam for diagnosis.	ANA ⊕ RF ⊖	**Most common presentation of JIA.** Usually diagnosed in young girls.
Polyarthritis	Present in **5 or more** joints; generally symmetric. Systemic symptoms rare.	RF positivity is rare (indicates severe disease). Young children may be ANA ⊕ with milder disease.	Rheumatoid nodules may be seen in children with RF ⊕ disease.
Systemic-onset (Still disease)	Recurrent high fever (> 39°C [> 102.2°F]). Hepatosplenomegaly. **Salmon-colored macular rash.**	ANA ⊖ RF ⊖	Joint inflamm tion may not occur for months to years after systemic symptoms appear.

History/Pe

Symptoms include ear pain, fever, crying, irritability, difficulty feeding or sleeping, vomiting, and diarrhea. Young children may **tug on their ears.**

Diagnosis

Signs on otoscopic exam reveal an erythematous tympanic membrane (TM), bulging or retraction of the TM and ↓ TM mobility (test with an insufflator bulb).

Treatment

- **High-dose amoxicillin** (80–90 mg/kg/day) × 10 days for empiric therapy. Resistant cases may require amoxicillin/clavulanic acid.
- Complications include TM perforation, mastoiditis, meningitis, cholesteatomas, and chronic otitis media. Recurrent otitis media can cause hearing loss with resultant speech and language delay. Chronic otitis media may require tympanostomy tubes.

BRONCHIOLITIS

An acute inflammatory illness of the small airways of the lower respiratory tract that primarily affects infants and children **< 2 years of age,** often in the **fall or winter. RSV is the most common cause;** others include parainfluenza, influenza, metapneumovirus, and other viruses. Progression to respiratory failure is a potentially fatal complication. Risk factors for severe RSV infection include age < 6 months, prematurity, heart or lung disease, neuromuscular disease, and immunodeficiency.

History/Pe

- Presents with:
  - Days 1–3: Low-grade fever, rhinorrhea, cough. Young infants might have apnea.
  - Days 4–6: Respiratory distress, tachypnea, hypoxia.
- Examination reveals **tachypnea, hypoxia,** intercostal retractions, **crackles or coarse breath sounds ("washing machine sounds"), ± wheezing.**
- An ↑ **respiratory rate** is the earliest and most sensitive vital sign change.

Diagnosis

- Predominantly a clinical diagnosis; routine cases do not need any lab or radiologic workup.
- In severe cases, a CXR can be obtained to rule out pneumonia and may show hyperinflation of the lungs with flattened diaphragms, interstitial infiltrates, and atelectasis.
- Nasopharyngeal aspirate to test for RSV and other viruses is highly sensitive and specific but has little effect on management (infants should be treated for bronchiolitis whether or not a virus is identified).

Treatment

- Treatment is **primarily supportive** with hydration, suctioning, and supplemental O_2.
- For patients with a history or strong family history of asthma, bronchodilators can be tried, and if they bring improvement of the patient's symptoms, then continued.
- Hospitalize if signs of severe illness are present.
- **Corticosteroids are not indicated.**

KEY FACT

RSV is the most common cause of bronchiolitis. Parainfuenza is the most common cause of croup.

KEY FACT

Young infants are at risk of apnea as a result of RSV bronchiolitis.

Q 1

A 4-day-old boy born at 34 weeks for intrauterine growth retardation has experienced frequent bilious vomiting for the past 24 hours and has passed stool mixed with bright red blood twice today. He initially fed well (consuming formula only) but now refuses the bottle. Examination is notable for lethargy, abdominal distention, and decreased bowel sounds. What is the most likely diagnosis, and what would you expect to see on abdominal radiography?

Q 2

A 2-year-old boy is brought to the pediatrician by his mother for a skin infection that started on his chin and rapidly spread to involve much of his face and neck. She complains that this is his third such infection this year, and that he is constantly plagued by sinus infections and bouts of pneumonia. There is no family history of recurrent infections. The patient appears uncomfortable, and dermatologic exam is notable for erosions coated in yellow crust that are widespread across the patient's face and neck. He also has patchy white pigmentation of the skin, light blonde hair, and blue eyes. What is the most likely diagnosis?

- **Ribavirin** is an antiviral drug sometimes used in high-risk infants with underlying heart, lung, or immune disease. **The American Academy of Pediatrics recommends against the use of ribavirin in otherwise healthy children.**
- **RSV prophylaxis** with injectable monoclonal antibodies (palivizumab) is recommended in autumn/winter for high-risk patients ≤ 2 years of age (eg, those with a history of prematurity, chronic lung disease, or congenital heart disease).

CROUP (LARYNGOTRACHEOBRONCHITIS)

An acute viral inflammatory disease of the larynx, primarily within the subglottic space. Pathogens include **parainfluenza virus types 1** (most common), **2,** and **3** as well as RSV, influenza, and adenovirus. Bacterial superinfection may progress to tracheitis.

History/Pe

Prodromal URI symptoms are typically followed by low-grade fever, mild dyspnea, **inspiratory stridor** that worsens with agitation, a hoarse voice, and a characteristic **barking cough** (which worsens at night).

Diagnosis

- Diagnosed by clinical impression; often based on the degree of stridor and respiratory distress.
- AP neck film may show the **classic "steeple sign" from subglottic narrowing** (see Figure 2.13-15), but this finding is **neither sensitive nor specific.**
- Table 2.13-14 differentiates croup from epiglottitis and tracheitis.

Treatment

- **Mild cases:** Outpatient management with cool mist therapy and fluids.
- **Moderate cases:** May require supplemental O_2, oral or **IM corticosteroids,** and **nebulized racemic epinephrine.**

1 **A**

This infant most likely has necrotizing enterocolitis, given his presentation and risk factors (prematurity, formula feeding). This is a serious diagnosis with up to 40% mortality. Findings on radiography can include pneumatosis intestinalis, air in the portal venous system, and free air under the diaphragm (in case of bowel perforation).

2 **A**

This child most likely has Chédiak-Higashi syndrome, due to autosomal recessive defects in the synthesis/maintenance of storage granules in a number of cell types (including leukocytes, platelets, neutrophils, and melanocytes). In addition to partial oculocutaneous albinism, these patients experience hepatosplenomegaly and recurrent, serious infections of the skin and respiratory tract by S aureus, S pyogenes, and Pneumococcus species. Chédiak-Higashi syndrome is often fatal in childhood because of overwhelming infection.

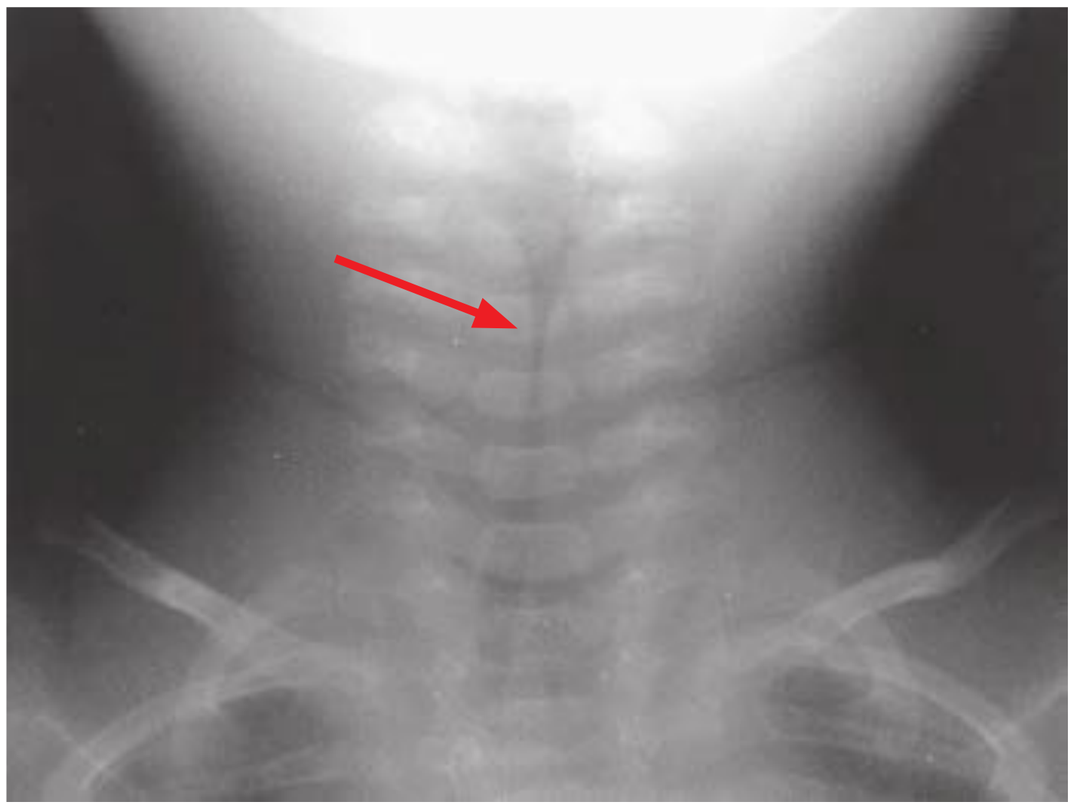


FIGURE 2.13-15. Croup. AP radiograph of the neck in this 1-year-old with inspiratory stridor and cough shows the classic "steeple sign" (arrow) consistent with the subglottic narrowing of laryngotracheobronchitis. (Reproduced with permission from Stone CK, Humphries RL. Current Diagnosis & Treatment: Emergency Medicine, 6th ed. New York, NY: McGraw-Hill; 2008.)

- **Severe cases** (eg, respiratory distress at rest, inspiratory stridor): Hospitalize and give **nebulized racemic epinephrine; consider intubation** if **there is danger of airway compromise.**

EPIGLOTTITIS

A **serious and rapidly progressive** infection of supraglottic structures (eg, the epiglottis and aryepiglottic folds). Prior to immunization, H in*fl*uenzae type b was the 1° pathogen. Common causes now include Streptococcus species, nontypeable H in*fl*uenzae, and viral agents.

History/Pe

- Presents with **acute-onset high fever** (39–40°C [102–104°F]), **dysphagia, drooling,** a muffled voice, **inspiratory retractions,** cyanosis, and soft stridor.
- Patients sit with the **neck hyperextended and the chin protruding** ("sniffing dog" position) and **lean forward in a "tripod" position** to maximize air entry.
- Untreated infection can rapidly lead to life-threatening airway obstruction and respiratory arrest.

Diagnosis

- Diagnosed by clinical impression. The differential diagnosis must include diffuse and localized causes of airway obstruction (see Tables 2.13-14 and 2.13-15).
- **The airway must be secured before a definitive diagnosis can be made.** In light of potential laryngospasm and airway compromise, **do not examine the throat unless an anesthesiologist or otolaryngologist is present.**
- Definitive diagnosis is made via direct fiberoptic visualization of a cherry-red, swollen epiglottis and arytenoids.
- Lateral x-ray film shows a swollen epiglottis obliterating the valleculae (**"thumbprint sign";** see Figure 2.13-16).

KEY FACT

Epiglottitis is a true emergency and can lead to life-threatening airway obstruction.

Treatment

- This disease is a **true emergency,** so time should not be wasted on ordering an x-ray film.
- Remember the ABCs; **secure the airway first** with endotracheal intubation or tracheostomy, and then give IV antibiotics (ceftriaxone or cefuroxime).

MENINGITIS

Bacterial meningitis most often occurs in children < 3 years of age; common organisms include S pneumoniae, N meningitidis, **and** E coli. **Enteroviruses** are the most common agents of viral meningitis and occur in children of all ages. Risk factors include sinofacial infections, trauma, immunodeficiency, and sepsis.

History/Pe

- Bacterial meningitis classically presents with the triad of **headache, high fever, and nuchal rigidity.**
- Viral meningitis is typically preceded by a prodromal illness that includes fever, sore throat, and fatigue.

Q

What are the most common causes of bacterial meningitis in neonates (< 1 month), infants/children, and adolescents?

TABLE 2.13-14. Characteristics of Croup, Epiglottitis, and Tracheitis

Variable	Croup	Epiglottitis	Tracheitis
Age group affected	3 months to 3 years.	3–7 years.	3 months to 2 years.
Incidence in children presenting with stridor	**88%.**	8%	2%
Pathogen	**Parainfluenza virus.**	H influenzae (nontypeable), S pneumoniae.	Often S aureus; commonly follows viral URI.
Onset	Prodrome (1–7 days).	Rapid (4–12 hours).	Prodrome (3 days) leading to acute decompensation (10 hours).
Fever severity	Low grade.	**High grade.**	Intermediate grade.
Associated symptoms	**Barking cough,** inspiratory stridor, hoarseness.	**Respiratory distress:** acute decompensation, toxic appearance, inspiratory stridor, muffled voice, drooling, tripoding.	Variable respiratory distress; slower onset than epiglottitis; pseudomembrane.
Position preference	None.	Seated, neck extended (tripod position).	None.
Response to racemic epinephrine	**Stridor improves.**	None.	None.
CXR finding	**"Steeple sign"** on AP film	**"Thumbprint sign"** on lateral film	**Subglottic narrowing.**

KEY FACT

Don't be fooled—neonates and young children rarely have meningeal signs on exam!

KEY FACT

Neonates should not be given ceftriaxone in light of the ↑ risk of biliary sludging and kernicterus.

A

- **Neonates:** Group B streptococci, E coli, Listeria.
- **Infants/children:** S pneumoniae, N meningitidis, H influenzae.
- **Adolescents:** N meningitidis, S pneumoniae.

- **Kernig sign** (reluctance of knee extension when the hip is flexed) and **Brudzinski sign** (hips are flexed in response to forced flexion of the neck) are nonspecific signs of meningeal irritation.
- Additional physical examination findings may include signs of ↑ **ICP** (papilledema, cranial nerve palsies) or a **petechial rash (**N meningitidis**).** Signs in neonates include lethargy, hyper- or hypothermia, **poor tone, a bulging fontanelle, and vomiting.**

Diagnosis

- Obtain a head CT to rule out ↑ ICP (risk of brainstem herniation) **if the patient is at high risk** (ie, exhibits neurologic deficits or has papilledema on funduscopic exam).
- Perform an LP; send cell count with differential, glucose and protein levels, Gram stain, and culture.

Treatment

- **Neonates** should receive **ampicillin and cefotaxime or gentamicin.** Consider **acyclovir** if there is concern for **herpes encephalitis** (eg, if the mother had HSV lesions at the time of the infant's birth or extremely bloody nontraumatic LP).
- **Older children** should receive **ceftriaxone and vancomycin.**

TABLE 2.13-15. Retropharyngeal vs Peritonsillar Abscess

Variable	Retropharyngeal abscess	Peritonsillar abscess
Age group affected	From 6 months to 6 years of age.	Usually > 10 years of age.
History/PE	**Acute-onset high fever** with sore throat, a muffle **"hot potato" voice,** trismus, drooling, and cervical lymphadenopathy. Usually unilateral; a mass may be seen in the posterior pharyngeal wall on visual inspection.	Sore throat, a muffle **"hot potato" voice,** trismus, drooling, **uvula displaced to opposite side.**
Pathogen	**Group A streptococcus** (most common), S aureus, Bacteroides (often polymicrobial).	**Group A streptococcus** (most common), S aureus, S pneumoniae, anaerobes.
Preferred position	Supine with the **neck extended** (sitting up or fl xing the neck worsens symptoms).	None.
Diagnosis	On **lateral neck x-ray film** the soft tissue plane should be ≤ 50% of the width of the corresponding vertebral body. Contrast CT of the neck helps dif erentiate abscess from cellulitis.	Usually **clinical.**
Treatment	Aspiration or incision and drainage of abscess; antibiotics.	Incision and drainage ± tonsillectomy; antibiotics.

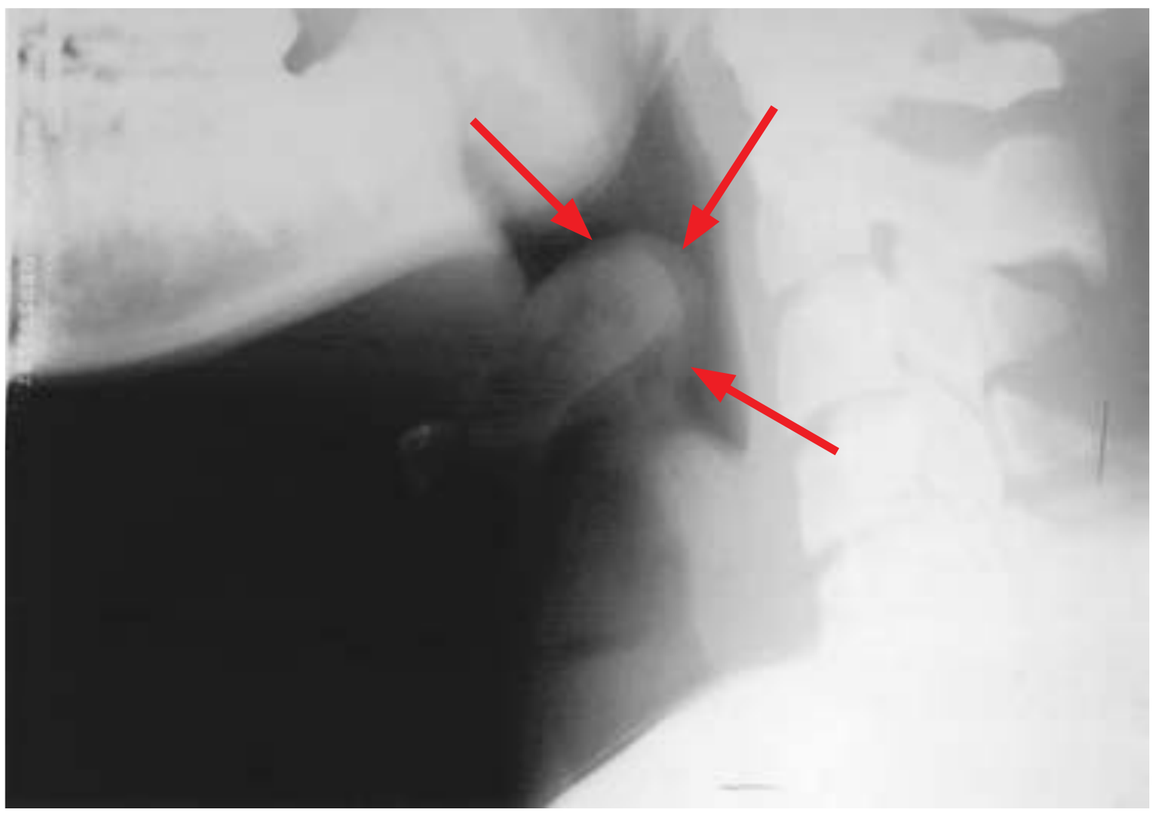


FIGURE 2.13-16. Epiglottitis. Lateral radiograph of the neck shows a markedly swollen epiglottis (arrows) demonstrating the classic "thumbprint sign," with near-complete airway obstruction. (Reproduced with permission from Stone CK, Humphries RL. Current Diagnosis & Treatment: Emergency Medicine, 6th ed. New York, NY: McGraw-Hill; 2008.)

OCULAR INFECTIONS OF THE NEONATE

Infectious conjunctivitis is transmitted as the neonate passes through the birth canal during labor, and the infection often presents during the first weeks of life. The most common causative agents include C trachomatis and HSV (usually HSV-2). N gonorrhoeae was much more common before the routine use of silver nitrate for prophylaxis; now it only causes < 1% of cases of neonatal conjunctivitis in the United States.

History/Pe

Table 2.13-16 summarizes the clinical presentation of common neonatal ocular infections.

Diagnosis

- **Bacterial cultures** and Gram stain are the gold standard for suspected gonococcal or chlamydial conjunctivitis.
- **HSV PCR is the diagnostic standard for children with corneal ulceration or those with a vesicular eruption anywhere on the body.**
- **The neonate's mother should undergo cervical Gram stain and culture if STI is the suspected cause of conjunctivitis.**

Treatment

- Empiric treatment can start before culture results are known.
- For chlamydial conjunctivitis, give **topical erythromycin ointment and oral erythromycin;** topical antibiotics alone are insufficient, as **systemic infection is often present.**
- For gonococcal conjunctivitis, give an **IV/IM third-generation cephalosporin.** Coverage of gonococcus is crucial if the causative agent is unknown, as **corneal ulceration** (and resultant scarring) can occur **within 24–48 hours!**
- For HSV conjunctivitis, treat with a 14- to 21-day course of **systemic acyclovir,** along with a topical agent (such as **vidarabine**).

PERTUSSIS (WHOOPING COUGH)

A highly infectious form of bronchitis caused by the gram-⊖ bacillus Bordetella pertussis. The DTaP vaccine (given in five doses in early childhood) is protective, but immunity wanes by adolescence. Adolescents and young

TABLE 2.13-16. Ocular Infections in the Neonatal Period

Causative agent	Characteristics
Ctrachomatis	Symptoms appear 1–2 weeks after birth. Presents with eyelid swelling and relatively scant watery discharge.
Ngonorrhoeae	Symptoms appear within 1 week of birth. Bilateral purulent conjunctivitis and marked eyelid edema. Tends to be more severe than chlamydial conjunctivitis.
HSV	Symptoms appear within 2 weeks of birth. Presents with conjunctival injection, watery/serosanguineous eye discharge and vesicular eruptions surrounding the eyes.

adults serve as the 1° reservoir for pertussis. Transmission is through aerosol droplets. Pertussis can be life-threatening for young infants but is generally a milder infection in older children and adults.

History/Pe

- Has **three stages:** (1) catarrhal (mild URI symptoms; lasts 1–2 weeks), (2) paroxysmal (paroxysms of cough with inspiratory whoop and posttussive emesis; lasts 2–3 months), and (3) convalescent (symptoms wane).
- Patients most often present in the paroxysmal stage but are most contagious in the catarrhal stage.
- The classic presentation is an **infant < 6 months of age with paroxysmal coughing, posttussive emesis, and apnea.**

Diagnosis

- Labs show an elevated WBC count with lymphocytosis (often ≥ 70%).
- **Nasopharyngeal culture is the gold standard.**

Treatment

- Hospitalize infants < 6 months of age.
- Give **azithromycin** × 10 days to patients. Exposed newborns are at high risk irrespective of their immunization status because they may not be entirely protected by maternal transplacental immunoglobulins.
- Close contacts (including daycare contacts) should receive prophylactic antibiotics (azithromycin × 5 days).



FIGURE 2.13-17. Fifth disease. Note the classic "slapped-cheek" appearance of fifth disease, which is caused by parvovirus B19. (Reproduced with permission from Wolff K, Johnson RA. Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology, 6th ed. New York, NY: McGraw-Hill; 2009.)

VIRAL EXANTHEMS

Table 2.13-17 outlines the clinical presentation of common viral exanthems.

TABLE 2.13-17. Viral Exanthems

Disease	Cause	Characteristics	Complications
Erythema infectiosum (fifth disease)	Parvovirus B19	**Prodrome:** None; fever is often absent or low grade. **Rash: "Slapped-cheek,"** pruritic, maculopapular, erythematous rash (see Figure 2.13-17). Starts on the arms and spreads to the trunk and legs. **Worsens with fever and sun exposure.**	**Arthropathy** in children and adults. Congenital infection is associated with fetal hydrops and death. **Aplastic crisis** may be precipitated in children with ↑ RBC turnover (eg, sickle cell anemia, hereditary spherocytosis) or in those with ↓ RBC production (eg, severe iron deficiency anemia).
Measles	Paramyxovirus	**Prodrome:** Low-grade fever with **C**ough, **C**oryza, and **C**onjunctivitis (the **"3 C's"**); **Koplik spots** (small irregular red spots with central gray specks) appear on the buccal mucosa after 1–2 days. **Rash:** An erythematous **maculopapular rash spreads from head to toe** (see Figure 2.13-18).	**Common:** Otitis media, pneumonia, laryngotracheitis. **Rare:** Subacute sclerosing panencephalitis.

(continues)

TABLE 2.13-17. Viral Exanthems (continued)

Disease	Cause	Characteristics	Complications
Rubella ("3-day measles")	Rubella virus	**Prodrome:** Asymptomatic or tender, generalized lymphadenopathy (clue: posterior auricular lymphadenopathy). **Rash:** Presents with an erythematous, tender maculopapular rash that **also spreads from head to toe.** **In contrast to measles, children with rubella often have only a low-grade fever and do not appear as ill.** Polyarthritis may be seen in adolescents.	Encephalitis, thrombocytopenia (a rare complication of postnatal infection). Congenital infection is associated with congenital anomalies (PDA, deafness, cataracts, intellectual disabilities).
Roseola infantum	HHV-6 and -7	**Prodrome:** Acute onset of high fever (> 40°C [> 104°F]); no other symptoms for 3–4 days. **Rash: A maculopapular rash appears as fever breaks** (begins on the trunk and quickly spreads to the face and extremities) and often lasts < 24 hours.	**Febrile seizures** may result from rapid fever onset.
Varicella (chickenpox)	VZV	**Prodrome:** Mild fever, anorexia, and malaise precede the rash by 24 hours. **Rash:** Generalized, pruritic, "teardrop" vesicles on red base; lesions are often at **different stages of healing.** Usually appears on the face and spreads to the rest of the body, sparing the palms and soles. Infectious from 24 hours before eruption until lesions crust over.	Progressive varicella with meningoencephalitis, pneumonia, and hepatitis in the immunocompromised. Skin lesions may develop 2° bacterial infections. Reye syndrome (associated with ASA use).
Varicella zoster	VZV	**Prodrome:** Reactivation of varicella infection; starts as pain along an affected sensory nerve. **Rash:** Pruritic "teardrop" vesicular rash in a **dermatomal** distribution. Uncommon unless the patient is **immunocompromised.**	Encephalopathy, aseptic meningitis, pneumonitis, TTP, Guillain-Barré syndrome, cellulitis, arthritis.
Hand-foot-and-mouth disease	Coxsackie A	**Prodrome:** Fever, anorexia, oral pain. **Rash:** Oral ulcers; maculopapular vesicular rash on the hands and feet and sometimes on the buttocks.	None (self-limited).

TORCHeS INFECTIONS

ToRCHeS infections refer to microbes that can be transmitted vertically (ie, from mother to fetus). Usually transplacental, but can occur perinatally (eg, HSV-2). May cause nonspecific signs such as growth retardation, hepatosplenomegaly, jaundice, and thrombocytopenia.

Table 2.13-18 outlines the common ToRCHeS infections.

TABLE 2.13-18. Common TORCHeS Infections

Agent	Mode of Transmission	Maternal Manifestations	Neonatal Manifestions
Toxoplasma gondii	Cat feces or ingestion of undercooked meat.	Usually asymptomatic; lymphadenopathy (rarely).	Classic triad: chorioretinitis, hydrocephalus, and intracranial calcifications, ± "blueberry muffin" rash.
Rubella	Respiratory droplets.	Rash, lymphadenopathy, arthritis.	Classic triad: PDA (or pulmonary artery hypoplasia), cataracts, and deafness, ± "blueberry muffin" rash.
CMV	Sexual contact, organ transplants.	Usually asymptomatic; mononucleosis-like illness.	Hearing loss, seizures, petechial rash, "blueberry muffin" rash, periventricular calcifications.
HIV	Sexual contact, needlestick.	Variable presentation depending on CD4+ count.	Recurrent infections, chronic diarrhea.
Herpes simplex virus-2	Skin or mucous membrane contact.	Usually asymptomatic; herpetic (vesicular) lesions.	Encephalitis, herpetic (vesicular) lesions.
Syphilis	Sexual contact.	Chancre (1°) and disseminated rash (2°) are the two stages likely to result in fetal infection.	Often results in stillbirth, hydrops fetalis; if child survives, presents with facial abnormalities (eg, notched teeth, saddle nose, short maxilla), saber shins, CN VIII deafness.

Reproduced with permission from Le T et al. First Aid for the USMLE Step 1 2015. New York, NY: McGraw-Hill; 2015.

Neonatology

APGAR SCORING

A rapid scoring system that helps evaluate the need for neonatal resuscitation (Table 2.13-19). Each of five parameters is assigned a score of 0–2 at 1 and 5 minutes after birth.

- **Scores of 8–10:** Typically reflect good cardiopulmonary adaptation.
- **Scores of 4–7:** Indicate the possible need for resuscitation. Infants should be observed, stimulated, and possibly given ventilatory support.
- **Scores of 0–3:** Indicate the need for immediate resuscitation.

CONGENITAL MALFORMATIONS

Table 2.13-20 describes selected congenital malformations.

NEONATAL JAUNDICE

An elevated serum bilirubin concentration (> 5 mg/dL) due to ↑ hemolysis or ↓ excretion. Subtypes are as follows:



FIGURE 2.13-18. Measles exanthem. A classic morbilliform exanthem is seen, with red papules spreading from the forehead and postauricular area to the neck, trunk, and extremities. (Reproduced with permission from Wolff K et al. Fitzpatrick's Dermatology in General Medicine, 7th ed. New York, NY: McGraw-Hill; 2008.)

TABLE 2.13-19. APGAR Scale (evaluate at 1 and 5 minutes postpartum)

Sign	2 points	1 point	0 points
Activity (muscle tone)	Active movement.	Arms and legs flexed.	Absent.
Pulse	> 100 bpm.	< 100 bpm.	Absent.
Grimace (reflex irritability)	**Active (sneezes, coughs, pulls away).**	**Some flexion of extremities.**	**Flaccid.**
Appearance (skin color)	Completely pink.	Pink body with blue extremities.	Blue/pale all over.
Respirations	Vigorous cry.	Slow, irregular respirations.	Absent.

KEY FACT

Omphalocele is sometimes associated with other congenital anomalies (as in Beckwith-Wiedemann syndrome); gastroschisis is not.

- **Conjugated (direct) hyperbilirubinemia:** Always pathologic.
- **Unconjugated (indirect) hyperbilirubinemia:** May be physiologic or pathologic. See Table 2.13-21 for differentiating characteristics.
- **Kernicterus:** A complication of unconjugated hyperbilirubinemia that results from irreversible bilirubin deposition in the basal ganglia, pons, and cerebellum. It typically occurs at levels of > 25–30 mg/dL and can be fatal. Risk factors include prematurity, asphyxia, and sepsis.

History/Pe

See Table 2.13-22.

- The history should focus on diet (breast milk or formula), intrauterine drug exposure, and family history (hemoglobinopathies, enzyme deficiencies, RBC defects).
- Physical examination may reveal signs of hepatic or GI dysfunction (abdominal distention, delayed passage of meconium, light-colored stools, dark urine), infection, or birth trauma (cephalohematomas, bruising, pallor, petechiae).
- **Kernicterus** presents with lethargy, poor feeding, a high-pitched cry, hypertonicity, and seizures; jaundice may follow a cephalopedal progression as bilirubin concentrations ↑.

Diagnosis

KEY FACT

Direct (conjugated) hyperbilirubinemia is always pathologic.

- For indirect hyperbilirubinemia, CBC with peripheral blood smear; blood typing of mother and infant (for ABO or Rh incompatibility); Coombs test and bilirubin levels.
- For direct hyperbilirubinemia, check LFTs, bile acids, blood cultures, sweat test, and tests for aminoacidopathies and α_1-antitrypsin deficiency. Ultrasound and/or hydroxy iminodiacetic acid (HIDA) scan can confirm suspected cholestatic disease.
- A jaundiced neonate who is febrile, hypotensive, and/or tachypneic needs a full sepsis workup and ICU monitoring.

Treatment

- Treat underlying causes (eg, infection).
- Treat **unconjugated hyperbilirubinemia** with **phototherapy** (for mild elevations) or **exchange transfusion** (for severe elevations > 20 mg/dL). Start

TABLE 2.13-20. Selected Congenital Malformations

Malformation	Presentation/diagnosis/treatment
Tracheoesophageal fistul	Tract between the trachea and esophagus. Associated with defects such as esophageal atresia and **VACTERL** (**V**ertebral, **A**nal, **C**ardiac, **T**racheal, **E**sophageal, **R**enal, **L**imb) anomalies. **Presentation: Polyhydramnios** in utero, ↑ oral secretions, inability to feed, gagging, aspiration pneumonia, respiratory distress. **Diagnosis:** CXR showing an NG tube coiled in the esophagus identifies esophageal atresia. The presence of air in the GI tract is suggestive; confirm with bronchoscopy. **Treatment:** Surgical repair.
Congenital diaphragmatic hernia	GI tract segments protrude through the diaphragm into the thorax; 90% are posterior left (Bochdalek). **Presentation:** Respiratory distress (from pulmonary hypoplasia and pulmonary hypertension); sunken abdomen; **bowel sounds over the left hemithorax.** **Diagnosis:** Ultrasound in utero; confirmed by postnatal CXR. **Treatment:** High-frequency ventilation or extracorporeal membrane oxygenation to manage pulmonary hypertension; surgical repair.
Gastroschisis	Herniation of the intestine only through the abdominal wall **next to the umbilicus (usually on the right) with no sac (the GI tract is exposed).** **Presentation:** Polyhydramnios in utero; often premature; associated with GI stenoses or atresia. Presents with erythematous, matted bowel. **Treatment:** Wrap exposed bowel with saline-soaked gauze, and secure with plastic immediately after birth. Surgical correction is needed in most cases.
Omphalocele	Herniation of abdominal viscera through the abdominal wall **at the umbilicus into a sac** covered by peritoneum and amniotic membrane (see Figure 2.13-19). **Presentation/diagnosis:** Polyhydramnios in utero; often premature; associated with other GI and cardiac defects. Seen in **Beckwith-Wiedemann syndrome and trisomies.** **Treatment:** C-section can prevent sac rupture; if the sac is intact, postpone surgical correction until the patient is fully resuscitated. **Keep the sac covered/stable** with petroleum and gauze. Intermittent NG suction to prevent abdominal distention.
Duodenal atresia	Complete or partial failure of the duodenal lumen to recanalize during gestational weeks 8–10. **Presentation:** Polyhydramnios in utero; **bilious emesis within hours after the first feeding.** Associated with **Down syndrome** and other cardiac/GI anomalies (eg, annular pancreas, malrotation, imperforate anus). **Diagnosis:** AXRs show the **"double bubble"** sign (air bubbles in the stomach and duodenum) proximal to the site of the atresia (see Figure 2.13-20). **Treatment:** Surgical repair.



FIGURE 2.13-19. Giant omphalocele in a newborn boy. Herniation of abdominal viscera through the abdominal wall at the umbilicus into a sac covered by peritoneum and amniotic membrane. (Reproduced with permission from Brunicardi FC et al. Schwartz's Principles of Surgery, 9th ed. New York, NY: McGraw-Hill; 2010.)



FIGURE 2.13-20. Duodenal atresia. Note the characteristic "double bubble" appearance of the duodenal bulb (1) and stomach (2) in a neonate with duodenal atresia presenting with bilious emesis. (Reproduced with permission from Brunicardi FC et al. Schwartz's Principles of Surgery, 9th ed. New York, NY: McGraw-Hill; 2010.)

TABLE 2.13-21. Physiologic vs Pathologic Jaundice

Physiologic jaundice	Pathologic jaundice
Not present in first 24 hours after birth.	Present in the first 24 hours of life.
Bilirubin ↑ < 0.5 mg/dL/day.	Bilirubin ↑ > 0.5 mg/dL/hr.
Bilirubin peaks at < 14–15 mg/dL.	Bilirubin peaks at > 15 mg/dL.
Direct bilirubin is < 10% of total.	Direct bilirubin is > 10% of total.
Resolves by 1 week in term infants and 2 weeks in preterm infants.	Persists beyond 1 week in term infants and 2 weeks in preterm infants.

phototherapy earlier (10–15 mg/dL) for preterm infants. **Phototherapy is not indicated for conjugated hyperbilirubinemia** and can lead to skin bronzing.

RESPIRATORY DISTRESS SYNDROME

KEY FACT

RDS is the most common cause of respiratory failure in preterm infants.

The most common cause of respiratory failure in **preterm** infants (affects > 70% of infants born at 28–30 weeks' gestation); formerly known as hyaline membrane disease. **Surfactant deficiency** leads to poor lung compliance, alveolar collapse, and atelectasis. Risk factors include maternal DM, male gender, and the second born of twins.

History/Pe

Presents in the **first 48–72 hours of life** with a respiratory rate > 60/min, progressive hypoxemia, cyanosis, nasal flaring, intercostal retractions, and expiratory grunting.

TABLE 2.13-22. Mechanisms of Neonatal Jaundice

Mechanism	Example(s)	Predominant bilirubin Species
Increased bilirubin production	Hemolysis (ABO or Rh incompatibility). Erythrocyte enzyme deficiency (G6PD deficiency). Erythrocyte structural defects (sickle cell anemia, hereditary spherocytosis). Ineffective erythropoiesis (thalassemias). Sepsis with DIC.	↑ unconjugated bilirubin.
Impaired hepatic uptake of bilirubin	Gilbert syndrome. Crigler-Najjar syndrome.	↑ unconjugated bilirubin.
Impaired bilirubin conjugation	Dubin-Johnson syndrome. Rotor syndrome. Newborn physiologic jaundice.	↑ conjugated bilirubin.
Increased enterohepatic circulation	Poor feeding. Breast milk jaundice. Pyloric stenosis.	↑ unconjugated bilirubin.

Diagnosis

- Check ABGs, CBC, and blood cultures to rule out infection.
- Diagnosis is clinical and confirmed with characteristic CXR findings (see Table 2.13-23).

Treatment

- **Continuous positive airway pressure (CPAP) or intubation and mechanical ventilation.**
- **Artificial surfactant** administration ↓ mortality.
- Pretreat mothers at risk for preterm delivery (< 30 weeks' gestation) with corticosteroids; if > 30 weeks, monitor fetal lung maturity via a lecithin-to-sphingomyelin (L/S) ratio and the presence of phosphatidylglycerol in amniotic fluid.

KEY FACT

An L/S ratio < 2:1 indicates a need for maternal glucocorticoid administration.

Complications

Persistent PDA, **bronchopulmonary dysplasia, retinopathy of prematurity,** barotrauma from positive pressure ventilation, intraventricular hemorrhage, and NEC are complications of treatment.

Pediatric Neurologic Disease

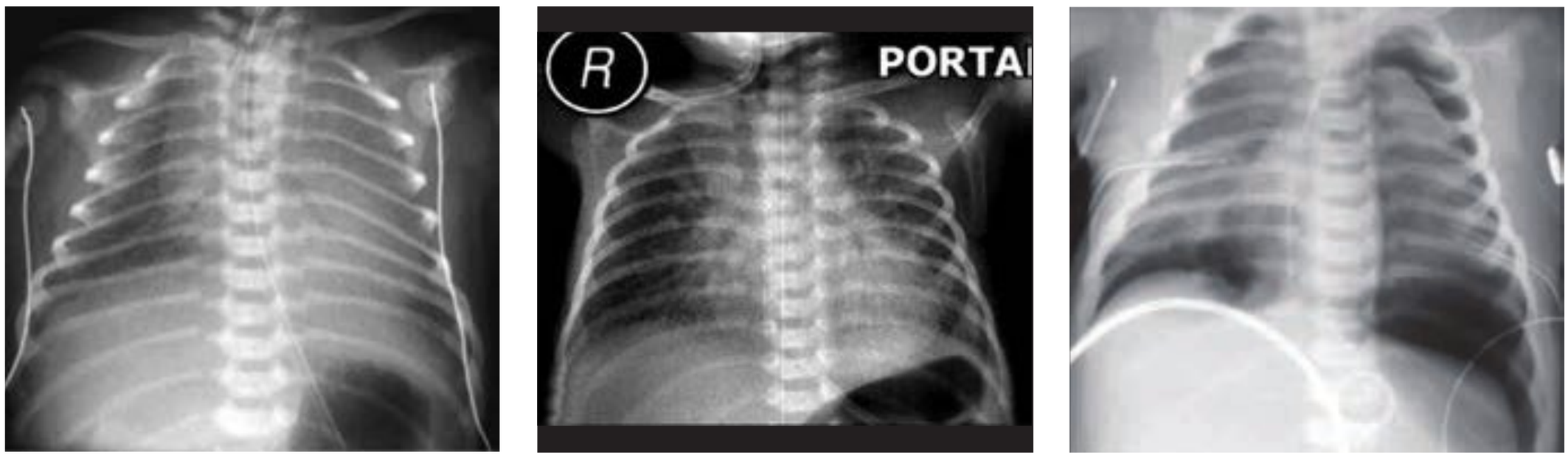
CEREBRAL PALSY

A range of **nonhereditary, nonprogressive disorders of movement and posture;** the most common movement disorder in children. Often results from **prenatal neurologic insult,** but in most cases the cause is unknown. Risk factors include low birth weight, intrauterine exposure to maternal infection, prematurity, perinatal asphyxia, trauma, brain malformation, and neonatal cerebral hemorrhage. Categories include the following:

- **Pyramidal (spastic):** Spastic paresis of any or all limbs. Accounts for 75% of cases. Intellectual disabilities are present in up to 90% of cases.
- **Extrapyramidal (dyskinetic):** A result of damage to extrapyramidal tracts. Subtypes are ataxic (difficulty coordinating purposeful movements), choreoathetoid, and dystonic (uncontrollable jerking, writhing, or posturing). Abnormal movements worsen with stress and disappear during sleep.

TABLE 2.13-23. CXR Findings in Neonatal Lung Pathology

Disease Process	Key Findings
Respiratory distress syndrome	Ground-glass appearance, **air bronchograms,** and lack of focal opacities (Figure 2.13-21A).
Transient tachypnea of the newborn (retained amniotic fluid in espiratory tract)	Perihilar streaking in interlobular fissures (Figure 2.13-21B).
Meconium aspiration	Coarse, irregular infiltrates, lung hyperexpansion and pneumothorax (Figure 2.13-21C).
Congenital pneumonia	Nonspecific patchy infiltrates.



A B C

FIGURE 2.13-21. Neonatal lung pathologies. (A) Chest radiograph of an intubated infant illustrating classic findings of respiratory distress syndrome. Note the granular or ground glass appearance of the lung parenchyma, the poor inflation, the lack of focal opacities, and the prominent air bronchograms. **(B)** Two-day-old child with transient tachypnea of the newborn, exhibiting perihilar streaking markings on chest radiography. **(C)** Bilateral pneumothorax and coarse, irregular infiltrates in a neonate with meconium aspiration. (Part A reproduced with permission from Tintinalli JE et al. Tintinalli's Emergency Medicine: A Comprehensive Study Guide, 7th ed. New York, NY: McGraw-Hill; 2010. Part B reproduced with permission from Alorainy IA, Barlas NB, Al-Boukai AA. Pictorial Essay: Infants of diabetic mothers, Indian J Radiol Imaging 2010 Aug;20(3):174-181. Part C reproduced with permission from Khan AN et al. Reading chest radiographs in the critically ill (Part I): Normal chest radiographic appearance, instrumentation and complications from instrumentation, Ann Thorac Med 2009 Apr;4(2):75-87.)

KEY FACT

The most common presenting symptom of cerebral palsy is delayed motor development.

History/Pe

- May be associated with seizure disorders, behavioral disorders, hearing or vision impairment, learning disabilities, and speech deficits.
- Affected limbs may show hyperreflexia, pathologic reflexes (eg, Babinski), ↑ tone/contractures, weakness, and/or underdevelopment. Definite hand preference before 1 year of age is a red flag.
- Toe walking and scissor gait are common. Hip dislocations and scoliosis may be seen.

Diagnosis

Diagnosed by clinical impression, although imaging can be used to determine the underlying cause of CP in some cases. For instance, ultrasonography may be useful in infants to identify intracranial hemorrhage or structural malformations, and MRI is diagnostic in older children. EEG may be useful in patients with suspected seizures.

Treatment

- There is **no cure for cerebral palsy.** Special education, physical therapy, braces, and surgical release of contractures may help.
- Treat spasticity with diazepam, dantrolene, or baclofen. Baclofen pumps and posterior rhizotomy may alleviate severe contractures.

FEBRILE SEIZURES

Usually occur in children between **6 months and 5 years of age** who have **no evidence of intracranial infection** or other causes. Risk factors include a rapid ↑ in temperature and a history of febrile seizures in a close relative. Febrile seizures recur in approximately one in three patients.

History/Pe

- Seizures usually **occur during the onset of fever** and may be the first sign of an underlying illness (eg, otitis media, roseola).

- Classified as simple or complex:
  - **Simple:** A **short-duration** (< 15-minute), **generalized** tonic-clonic seizure with one seizure in a 24-hour period, and returning to neurologic baseline shortly after. A high fever (> 39°C [> 102.2°F]) and fever onset within hours of the seizure are typical.
  - **Complex:** A **long-duration** (> 15-minute) or **focal** seizure or multiple seizures in a 24-hour period or not returning to neurologic baseline. A low-grade fever for several days before seizure onset may be present.

Diagnosis

- Focus on finding a source of infection. LP is indicated if there are clinical signs of CNS infection (eg, altered consciousness, meningismus, a tense/bulging anterior fontanelle) after ruling out ↑ ICP.
- No workup is necessary for first-time simple febrile seizures, and no lab studies are needed if presentation is consistent with febrile seizures in children > 18 months of age. Infants < 6 months of age need a sepsis workup (CBC, UA, and blood, urine, and CSF culture).
- For atypical presentations, obtain electrolytes, serum glucose, blood cultures, UA, and CBC with differential.

KEY FACT

Perform an LP if CNS infection is suspected in a patient with a febrile seizure.

Treatment

- Use **antipyretic therapy** (acetaminophen; **avoid ASA in light of the risk of Reye syndrome**) and treat any underlying illness. Note that antipyretic therapy does not ↓ the recurrence of febrile seizures.
- For complex seizures, perform a thorough neurologic evaluation, including an EEG and an MRI. Chronic anticonvulsant therapy (eg, diazepam or phenobarbital) may be necessary.

Complications

- The risk of recurrence is < 30% and is highest within 1 year of the initial episode. For simple febrile seizures, there is no ↑ risk of developmental abnormalities or epilepsy.
- Risk factors for the development of epilepsy include complex febrile seizures (~ 10% risk), ⊕ family history of epilepsy, an abnormal neurologic exam, and developmental delay.

KEY FACT

Simple febrile seizures do **not** cause brain damage, usually do **not** recur, and do **not** lead to an ↑ risk of epilepsy.

Pediatric Oncology

LEUKEMIA

A hematopoietic malignancy of lymphocytic or myeloblastic origin. The most common childhood malignancy; 97% of cases are acute leukemias (ALL > AML). ALL is most common in white boys between 2 and 5 years of age; AML is seen most frequently in black boys throughout childhood. Associated with trisomy 21, Fanconi anemia, prior radiation, SCID, and congenital bone marrow failure states.

KEY FACT

ALL is the most common childhood malignancy, followed by CNS tumors and lymphomas.

History/Pe

- Symptoms are abrupt in onset. They are initially nonspecific (anorexia, fatigue) and are followed by **bone pain with limp or refusal to bear weight, fever (from neutropenia), anemia, ecchymoses, petechiae, and/or hepatosplenomegaly.**
- CNS metastases may be associated with headache, vomiting, and papilledema.

- AML can present with a chloroma, a greenish soft-tissue tumor on the skin or spinal cord.

Diagnosis

- CBC, coagulation studies, and peripheral blood smear, which shows high numbers of blasts (lymphoblasts are found in 90% of cases). **WBC counts can be low, normal, or high.**
- A **bone marrow aspirate and biopsy** for immunophenotyping (TdT assay and a panel of monoclonal antibodies to T- and B-cell antigens) and genetic analysis are necessary to confirm the diagnosis. The diagnosis is made if bone marrow is hypercellular with ↑ lymphoblasts.
- **CXR to rule out a mediastinal mass.**

Treatment

- Chemotherapy based, including induction, consolidation, and maintenance phases.
- **Tumor lysis syndrome** is common during the initiation of treatment of cancers with high cell turnover (such as leukemias and lymphomas). It is caused by the lysis of many neoplastic cells in a short period of time, resulting in the release of cell contents into the bloodstream. It is characterized by hyperkalemia, hyperphosphatemia, hyperuricemia, and hypocalcemia (as calcium is bound by phosphate released from the neoplastic cells). It can result in renal failure, arrhythmias, and death. Treat with fluids, diuretics, and allopurinol (which reduces the risk of urate-induced nephropathy). **Corticosteroids may** precipitate tumor lysis syndrome.

KEY FACT

Watch for tumor lysis syndrome at the onset of any chemotherapy regimen.

NEUROBLASTOMA

An embryonal tumor of neural crest origin. More than half of patients are **< 2 years of age,** and 70% have distant metastases at presentation. Associated with **neurofibromatosis, Hirschsprung disease,** and the N-myc oncogene.

History/Pe

- Lesion sites are most commonly abdominal, thoracic, and cervical (in descending order).
- Symptoms may vary with location and may include a **nontender abdominal mass (may cross the midline), Horner syndrome,** hypertension, or cord compression (from a paraspinal tumor).
- Patients may have anemia, FTT, and fever.
- More than 50% of patients will have metastases at diagnosis. Signs include bone marrow suppression, proptosis, hepatomegaly, subcutaneous nodules (Figure 2.13-22), and **opsoclonus/myoclonus.**

Diagnosis

- **Fine-needle aspirate of tumor.** Histologically appears as small, round, blue tumor cells with a characteristic rosette pattern.
- **Elevated 24-hour urinary catecholamines (vanillylmandelic acid and homovanillic acid).**
- CT scan, bone scan, and bone marrow aspirate: **for staging.**

Treatment

Local excision plus postsurgical chemotherapy vand/or radiation.



FIGURE 2.13-22. Neuroblastoma presenting with multiple subcutaneous nodules.
(Reproduced with permission of the Armed Forces Institute of Pathology, Atlas *of* Tumor Pathology.)

WILMS TUMOR

A renal tumor of embryonal origin that is most commonly seen in **children 2–5 years** of age. Associated with **Beckwith-Wiedemann syndrome** (hemihypertrophy, macroglossia, visceromegaly), **neurofibromatosis, and WAGR syndrome** (**W**ilms tumor, **A**niridia, **G**enitourinary abnormalities, mental **R**etardation (now called "intellectual disabilities").

History/Pe

- Presents as an **asymptomatic, nontender,** smooth abdominal mass that **does not usually cross the midline.**
- Abdominal pain, fever, hypertension, and microscopic or gross hematuria are seen.

Diagnosis

- Biopsy or fine-needle aspiration is required for definitive diagnosis.
- Abdominal ultrasonography.
- CT scans of the chest and abdomen are used to detect metastases.

Treatment

Local resection and nephrectomy with postsurgical chemotherapy and radiation depending on stage and histology.

CHILDHOOD BONE TUMORS

It is critical to distinguish between Ewing sarcoma and osteosarcoma (see Table 2.13-24 and Figure 2.13-23).

Pediatric Musculoskeletal Disorders

COMMON PEDIATRIC ORTHOPEDIC INJURIES

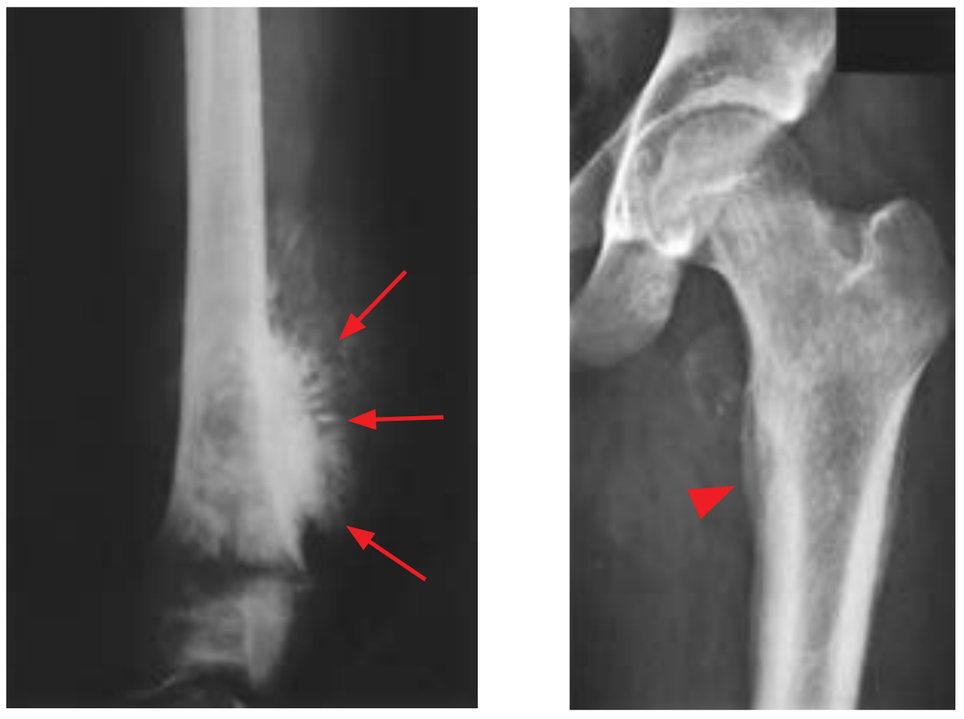
Table 2.13-25 outlines the presentation and treatment of common pediatric orthopedic injuries.

Q

A 2-year-old girl is brought to the pediatrician by her mother for increasing irritability and a 4-pound weight loss in the last month. Physical exam is notable for a well-defined, nodular mass in the left flank that crosses the midline. What is the most likely diagnosis?

TABLE 2.13-24. Ewing Sarcoma vs Osteosarcoma

Variable	Ewing Sarcoma	Osteosarcoma
Origin	Sarcoma (neuroectoderm); associated with chromosome 11:22 translocation.	Osteoblasts (mesenchyme).
Epidemiology	Commonly seen in **white** male adolescents.	Commonly seen in male adolescents.
History/PE	Local pain and swelling. **Systemic symptoms** (fever, anorexia, fatigue) are common.	Local pain and swelling. Systemic symptoms are rare.
Location	**Midshaft** of long bones (femur, pelvis, fibula, humerus)	**Metaphyses** of long bones (distal femur, proximal tibia, proximal humerus). Metastases to lungs in 20%.
Diagnosis	Leukocytosis, ↑ ESR. Lytic bone lesion with **"onion skin"** periosteal reaction on plain x-ray film	**↑ alkaline phosphatase.** **"Sunburst" lytic bone lesions.** Chest CT to rule out pulmonary metastases.
Treatment	Local excision, chemotherapy, and radiation.	Local excision, chemotherapy.



A B

FIGURE 2.13-23. Malignant bone tumors. (A) Osteosarcoma. Femoral radiograph shows the typical "sunburst" appearance of osteosarcoma (arrows). **(B)** Ewing sarcoma. The characteristic "onion skinning" of Ewing sarcoma (arrowhead) is evident in the proximal femur in this radiograph of the left hip. (Reproduced with permission from Kantarjian HM et al. MD Anderson Manual of Medical Oncology. New York, NY: McGraw-Hill; 2006.)

A

This patient most likely has neuroblastoma arising from the left adrenal gland. It is the most common solid tumor of childhood and is derived from neural crest cells. Unlike Wilms tumor (nephroblastoma), neuroblastoma is accompanied by systemic symptoms and often crosses the midline. The majority of children have metastases at the time of diagnosis.

TABLE 2.13-25. Orthopedic Injuries in Children

Injury	Mechanics	Treatment
Clavicular fracture	The most commonly fractured long bone in children. May be **birth related** (especially in large infants); can be associated with **brachial plexus** palsies and subclavian artery injury. Usually involves the middle third of the clavicle, with the proximal fracture end displaced superiorly as a result of the pull of the sternocleidomastoid.	Sling.
Greenstick fracture	Incomplete fracture involving the cortex of only 1 side (tension/trauma side) of the bone.	Reduction with casting. Order films t 10–14 days.
Nursemaid's elbow	**Radial head subluxation.** Secondary to being pulled or lifted by the hand. Pain, pronation, and refusal to bend the elbow.	**Manual reduction** by gentle supination of the elbow at 90 degrees of fl xion. No immobilization.
Torus fracture	**Buckling** of the compression side of the cortex 2° to trauma. Usually occurs in the distal radius or ulna as a result of a fall.	Cast immobilization for 3–5 weeks.
Supracondylar humerus fracture	**The most common pediatric elbow fracture.** Tends to occur at 5–8 years of age. Proximity to the brachial artery ↑ the **risk of Volkmann contracture** (results from compartment syndrome of the forearm). Beware of **brachial artery entrapment** (check radial pulse). See Figure 2.13-24.	Cast immobilization; closed reduction with percutaneous pinning if significa tly displaced.
Osgood-Schlatter disease	**Overuse** apophysitis of the tibial tubercle. Causes localized pain, especially with quadriceps contraction, in active young boys.	↓ activity for 2–3 months or until asymptomatic. Neoprene brace for symptomatic relief.
Salter-Harris fracture	Fractures of the growth plate in children. Classified y fracture pattern: **I:** Physis (growth plate). **II:** Metaphysis and physis. **III:** Epiphysis and physis. **IV:** Epiphysis, metaphysis, and physis. **V:** Crush injury of the physis.	Closed vs open reduction to obtain appropriate alignment, followed by immobilization.

DUCHENNE MUSCULAR DYSTROPHY

An **X-linked recessive disorder** resulting from a deficiency of **dystrophin,** a cytoskeletal protein. Onset is usually at 3–5 years of age. Female carriers can be symptomatic depending on severity of disease.

History/Pe

- Affects axial and proximal muscles more than distal muscles.
- May present with progressive **clumsiness, fatigability,** difficulty standing or walking, difficulty walking on toes (gastrocnemius shortening), **Gowers maneuver** (using the hands to push off the thighs when rising from the floor), and waddling gait.
- **Pseudohypertrophy of the gastrocnemius muscles** is also seen.
- Intellectual disabilities are common.

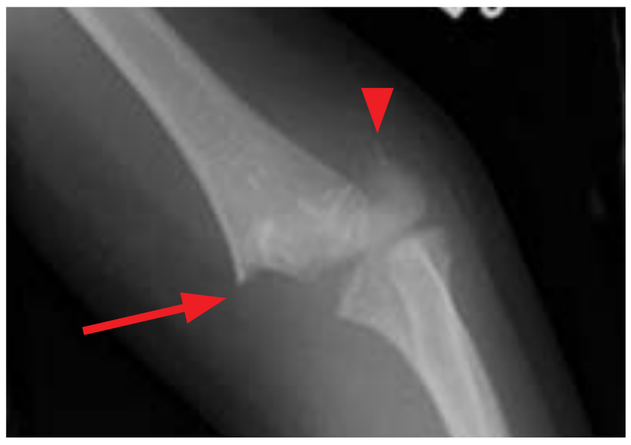


FIGURE 2.13-24. Supracondylar humerus fracture. Radiograph of the left elbow shows a medial supracondylar humerus fracture (arrow) with displacement of the distal fracture fragment (arrowhead) following trauma in a 9-year-old boy. (Reproduced with permission from USMLE-Rx.com.)

- Table 2.13-26 outlines the differential diagnosis of DMD and Becker muscular dystrophy.

Diagnosis

- **Muscle biopsy** shows necrotic muscle fibers with **absence of dystrophin protein.**
- ⊖ **dystrophin immunostain;** ↑ CK.
- EMG shows polyphasic potentials and ↑ recruitment.

Treatment

Physical therapy is necessary to maintain ambulation and to prevent contractures. Liberal use of tendon release surgery may prolong ambulation.

Complications

Mortality is due to high-output cardiac failure (stemming from cardiac fibrosis).

DEVELOPMENTAL DYSPLASIA OF THE HIP

Also called congenital hip dislocation; can result in subluxed or dislocated femoral heads, leading to early degenerative joint disease. Dislocations result from poor hip development due to lax musculature and **excessive uterine packing** in flexed and adducted position (eg, breech presentation), leading to excessive stretching of posterior hip capsule and contractures.

History/PE

- Most commonly found in **firstborn girls** born in the **breech position.** ↑ risk with family history.
- **Barlow maneuver:** Posterior pressure is placed on inner aspect of the abducted thigh, and hip is then adducted, leading to an audible "clunk" as the femoral head dislocates posteriorly.
- **Ortolani maneuver:** Thighs are gently abducted from the midline with anterior pressure on the greater trochanter. **Soft click** signifies reduction of femoral head into acetabulum.
- **Allis (Galeazzi) sign:** The knees are at unequal heights when the hips and knees are flexed (the dislocated side is lower).
- **Asymmetric inguinal skin folds** that extend beyond the anus and limited abduction of the affected hip are also seen.

TABLE 2.13-26. DMD vs Becker Muscular Dystrophy

Variable	DMD	Becker Muscular Dystrophy
Onset	3–5 years.	5–15 years and beyond.
Life expectancy	Teens.	30s–40s.
Intellectual disabilities	Common.	Uncommon.
Western blot	Dystrophin is markedly ↓ or absent.	Dystrophin levels are normal, but protein is abnormal.

Diagnosis

- **Early detection is critical** to allow for proper hip development.
- Ultrasonography prior to 6 months of age given lack of ossification of femoral head.
- Radiographs appropriate at > 4–6 months of age.

Treatment

- Begin treatment early. May self-resolve prior to 2 weeks of age.
- **< 6 months:** Splint with a **Pavlik harness** (maintains the hip flexed and abducted). To prevent avascular necrosis (AVN), do not flex the hips > 60 degrees.
- **6–15 months:** Spica cast.
- **15–24 months:** Open reduction followed by spica cast.

Complications

- Joint contractures and AVN of the femoral head.
- Without treatment, a significant defect is likely in patients < 2 years of age.

LEGG-CALVÉ-PERTHES DISEASE

Idiopathic AVN and osteonecrosis of the femoral head (see Figure 2.13-25). Most common in boys 4–10 years of age. Usually a self-limited disease, with symptoms lasting < 18 months.

History/Pe

- Generally asymptomatic at first, but patients can develop a **painless limp,** antalgic gait and thigh muscle atrophy.
- If pain is present, it can be in the groin or anterior thigh, or it may be referred to the knee.



A B

FIGURE 2.13-25. Legg-Calvé-Perthes disease. AVN of the femoral head. (Reproduced with permission from Skinner HB. Current Diagnosis & Treatment in Orthopedics, 2nd ed. Stamford, CT: Appleton & Lange; 2000.)

- **Limited abduction and internal rotation;** atrophy of the affected leg.
- Usually unilateral (85–90%).

Diagnosis

Initial radiographs can be normal but later can show flattened and fragmented femoral head.

Treatment

- Observation sufficient if limited femoral head involvement or if full ROM is present.
- If extensive or ↓ ROM, consider bracing, hip abduction with a Petrie cast, or an osteotomy.
- The prognosis is good if the patient is < 6 years of age and has full ROM, ↓ femoral head involvement, and a stable joint.

SLIPPED CAPITAL FEMORAL EPIPHYSIS

Displacement of the femoral epiphysis from the femoral neck, through the growth plate. The name is misleading, because the epiphysis remains within the acetabulum while the metaphysis moves anteriorly and superiorly. Presents in **obese** children ages 10–16. Associated with hypothyroidism and other endocrinopathies.

History/Pe

- Insidious onset of dull hip pain, or referred knee pain, and a **painful limp.**
- Restricted ROM and **inability to bear weight** (differentiates unstable from stable SCFE).
- Bilateral in 40–50% of cases.
- Limited internal rotation and abduction of the hip. Patients hold hip in passive external rotation.

Diagnosis

- Radiographs of **both** hips in **AP and frog-leg lateral views** reveal **posterior and inferior displacement** of the femoral head (see Figure 2.13-26).
- In patients under the 10th percentile of height, rule out hypothyroidism with TSH.

Treatment

- The disease is progressive, so treatment should begin promptly.
- Immediate surgical screw fixation to reduce risk of AVN.
- **No weight bearing** should be allowed until the defect is surgically stabilized.

Complications

Chondrolysis, AVN of the femoral head, and premature hip osteoarthritis requiring arthroplasty.

MNEMONIC

Differential diagnosis of ediatric limp—

STARTSS HOTT

Septic joint
Tumor
Avascular necrosis (Legg-Calvé-Perthes)
Rheumatoid arthritis/JIA
Tuberculosis
Sickle cell disease
SCFE
Henoch-Schönlein purpura
Osteomyelitis
Trauma
Toxic synovitis

KEY FACT

Legg-Calvé-Perthes disease typically presents as painLESS, while SCFE can be painFULL.

SCOLIOSIS

A **lateral curvature of the spine** > 10 degrees. It is sometimes associated with kyphosis or lordosis. **Most commonly idiopathic,** developing in early adolescence. Other etiologies are congenital or associated with neuromuscular, vertebral, or spinal cord disease. The male-to-female ratio is 1:7 for curves that progress and require treatment.

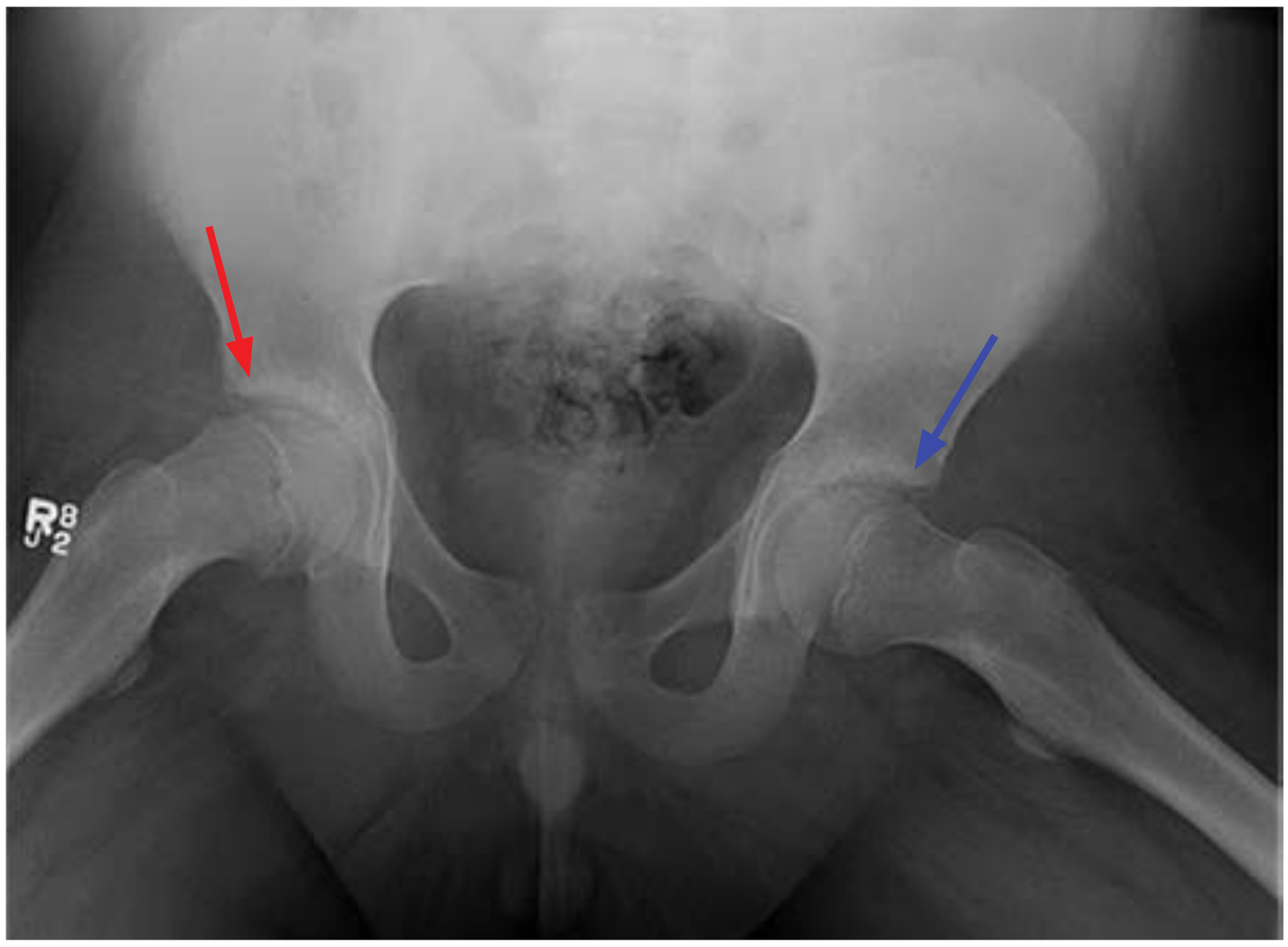


FIGURE 2.13-26. Slipped capital femoral epiphysis. Frog-leg AP radiograph demonstrates medial and inferior displacement of the right femoral epiphysis (red arrow) relative to the femoral neck. In comparison, the left side (blue arrow) is normal. (Reproduced with permission from USMLE-Rx.com.)

History/Pe

- Idiopathic disease is usually identified during school physical screening.
- Vertebral and rib rotation deformities are accentuated by the Adams forward bending test.

Diagnosis

Radiographs of the spine (posterior, anterior, and full-length views).

Treatment

- Close observation for < 20 degrees of curvature.
- Spinal bracing for 20–49 degrees of curvature in patients with remaining growth. **Curvature may progress even with bracing.**
- Surgical correction for > 50 degrees of curvature.

Complications

Severe scoliosis can create restrictive lung disease.

Well-Child Care

ANTICIPATORY GUIDANCE

An important aspect of every well-child visit. Commonly tested advice includes the following:

- Keep the water heater at < 48.8°C (< 120°F).
- Babies should **sleep on their backs** without any stuffed animals or other toys in the crib (to ↓ the risk of SIDS).

KEY FACT

SIDS = sudden infant death syndrome.
Most common cause of unexplained death in children < 1 year old.
Unknown pathogenesis.
ALTE = apparent life-threatening event (ie, unexpected and frightening change in appearance or behavior).
No longer thought to be a precursor of SIDS.

- Car safety seats should be **rear facing** and should be placed in the back of the car (seats can face forward if the child is > 2 years of age and weighs > 40 pounds).
- No solid foods should be given before 6 months; they should then be introduced gradually and one at a time. Do not give cow's milk prior to 12 months.
- Syrup of ipecac (an emetic) is no longer routinely recommended for accidental poisoning. Poison control should be contacted immediately for assistance.

HEARING AND VISION SCREENING

KEY FACT

Leukocoria indicates retinoblastoma, congenital cataracts, or retinopathy of prematurity.

- Objective hearing screening (otoacoustic emissions and/or auditory brainstem response) for newborns prior to discharge is common.
- Objective hearing screening is indicated for children with a history of meningitis, ToRCHeS infections, measles and mumps, and recurrent otitis media.
- The red reflex should be checked at birth. Leukocoria is the lack of a red reflex and can indicate the presence of retinoblastoma. Can also be an incidental finding in a baby's first photos.
- **Strabismus** (ocular misalignment) is normal until 3 months of age; beyond 3 months, children should be evaluated by a pediatric ophthalmologist and may require corrective lenses, occlusion, and/or surgery to prevent **amblyopia** (suppression of retinal images in a misaligned eye, leading to permanent vision loss).

CHILDHOOD VACCINATIONS

The Epidemiology chapter summarizes CDC-recommended vaccinations for the pediatric population. Contraindications and precautions in this population are as follows:

- **Contraindications:**
  - Severe allergy to a vaccine component or a prior dose of vaccine. **Patients who have life-threatening allergies to eggs may not receive MMR.**
  - Encephalopathy within 7 days of prior pertussis vaccination.
  - Avoid live vaccines (oral polio vaccine, varicella, MMR) in immunocompromised and pregnant patients (exception: HIV patients may receive MMR and varicella).
- **Precautions:**
  - Current moderate to severe illness (with or without fever).
  - Prior reactions to pertussis vaccine (fever > 40.5°C [> 104.9°F]), a shocklike state, persistent crying for > 3 hours within 48 hours of vaccination, or seizure within 3 days of vaccination.
  - A history of receiving IVIG in the past year.
- The following are **not** contraindications to vaccination:
  - Mild illness and/or low-grade fever.
  - Current antibiotic therapy.
  - Prematurity.

LEAD POISONING

Most exposure in children is due to lead-contaminated household dust from **lead paint.** Screening should be routinely performed at 12 and 24 months for patients living in high-risk areas (pre-1950s homes or zip codes with high

percentages of elevated blood lead levels); universal screening is not recommended.

History/Pe

- Presents with irritability, headache, hyperactivity or apathy, anorexia, **intermittent abdominal pain,** constipation, intermittent vomiting, and **peripheral neuropathy (wrist or foot drop).**
- Acute encephalopathy (usually with levels > 70 µg/dL) is characterized by ↑ ICP, vomiting, confusion, seizures, and coma.

Diagnosis

- Do a fingerstick test as an initial screen at age 1 or 2; then obtain serum lead level.
- CBC and peripheral blood smear show **microcytic, hypochromic anemia and basophilic stippling (Figure 2.13-27). Sideroblastic anemia may also be present.**

Treatment

- **< 45 µg/dL and asymptomatic:** Retest at 1–3 months; remove sources of lead exposure.
- **45–69 µg/dL:** Chelation therapy (inpatient **EDTA** or outpatient oral succimer **[DMSA]**).
- **≥ 70 µg/dL:** Chelation therapy (inpatient **EDTA** + **BAL** [IM dimercaprol]).

KEY FACT

New evidence has shown impaired intelligence and neurodevelopmental outcomes among children exposed to lead levels as low as 10 µg/dL.

Pediatric Urology

VESICOURETERAL REFLUX

Retrograde projection of urine from the bladder to the ureters and kidneys. May be due to posterior urethral valves, urethral or meatal stenosis, or a neurogenic bladder. Classified as follows:

- **Mild reflux (grades I–II):** No ureteral or renal pelvic dilation. Often resolves spontaneously.

KEY FACT

Posterior urethral valves are the most common congenital urethral obstruction. Classic findings are a male infant with a distended, palpable bladder and low urine output.

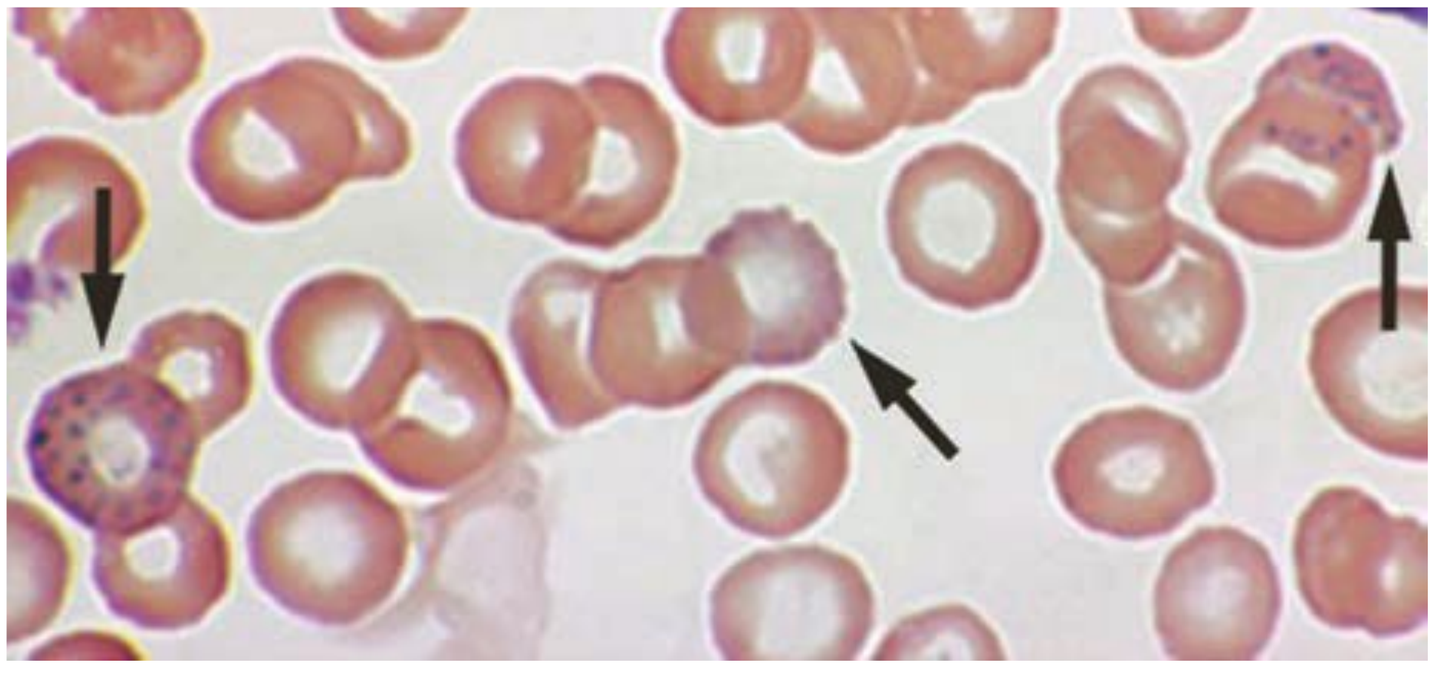


FIGURE 2.13-27. Basophilic stippling (arrows) in lead poisoning. (Used with permission of Dr. Herbert L. Fred and Hendrik A. van Dijk.)



FIGURE 2.13-28. Vesicoureteral reflux Frontal radiograph from a voiding cystourethrogram shows reflux to the left ureter and intrarenal collecting system with hydronephrosis. Note the absence of reflux on the normal right side. (Reproduced with permission from Doherty GM. Current Diagnosis & Treatment: Surgery, 13th ed. New York, NY: McGraw-Hill; 2010.)

- **Moderate to severe reflux (grade III–V):** Ureteral dilation with associated caliceal blunting in severe cases.

History/Pe

Patients present with recurrent UTIs, typically in childhood. Prenatal ultrasonography may identify hydronephrosis and/or oligohydramnios.

Diagnosis

Obtain a **voiding cystourethrogram** (VCUG) to detect abnormalities at ureteral insertion sites and to classify the grade of reflux (see Figure 2.13-28). VCUG should also be performed if there is recurrence of febrile UTI.

Treatment

- Treat infections aggressively. Treat mild reflux with daily prophylactic antibiotics (amoxicillin if < 2 months of age; otherwise TMP-SMX or nitrofurantoin) until reflux resolves.
- Surgery (ureteral reimplantation) is generally reserved for children with persistent high-grade (III to V) reflux. Inadequate treatment can lead to progressive **renal scarring** and end-stage renal disease.

KEY FACT

For children 2–24 months of age with multiple urinary tract infections, they should first have an ultrasound exam and then have a VCUG only if ultrasonography shows hydronephrosis, scarring, or other findings suspicious for obstruction or high grade VUR. Evidence is limited for children < 2 months.

CRYPTORCHIDISM

Failure of one or both of the testes to fully descend into the scrotum. **Low birth weight is a risk factor.**

History/Pe

Bilateral cryptorchidism is associated with prematurity, oligospermia, congenital malformation syndromes (Prader-Willi, Noonan syndromes), and infertility. Associated with an ↑ **risk of testicular malignancy.**

Diagnosis

The testes **cannot be manipulated into the scrotal sac** with gentle pressure (vs retractile testes) and can be palpated anywhere along the inguinal canal or in the abdomen.

KEY FACT

Bringing the testes into the scrotum may ↓, but not eliminate, the risk of testicular cancer.

Treatment

- **Orchiopexy** for prepubertal boys; orchiectomy if discovered after puberty to minimize the risk of testicular cancer.
- If discovered later, consider orchiectomy to prevent testicular cancers vs close observation.

HIGH-YIELD FACTS IN

PSYCHIATRY

Childhood and Adolescent Disorders 422
- Attention-deficit hyperactivity disorder 422
- Autism spectrum disorder 422
- disruptive behavioral disorders 423
- Intellectual developmental disorder 423
- Tourette syndrome 423

Psychotic Disorders 424
- Schizophrenia 424

Anxiety Disorders 425
- Generalized Anxiety disorder 425
- Panic disorder 426
- Phobias (Social and Specific) 427

Obsessive-Compulsive Disorder and Related Disorders 428
- obsessive-compulsive disorder 428
- Body dysmorphic disorder 429

Trauma and Stressor-Related Disorders 429
- Posttraumatic Stress disorder 429
- Adjustment disorder 430

Neurocognitive Disorders 430
- dementia (aka Major Neurocognitive disorder) 430
- delirium 431

Mood Disorders 432
- Major depressive disorder 432
- Bipolar disorder 434

Personality Disorders 436

Substance Use Disorders 438
- Alcohol Use disorder 438

Eating Disorders 440
- Anorexia Nervosa 440
- Bulimia Nervosa 442

Miscellaneous Disorders 442
- Sexual disorders 442
- Sleep disorders 443
- Somatic Symptom and Related disorders 445
- Factitious disorders and Malingering 445
- Sexual and Physical Abuse 446
- Suicidality 446

Childhood and Adolescent Disorders

ATTENTION-DEFICIT HYPERACTIVITY DISORDER

KEY FACT

Children must exhibit ADHD symptoms in two or more settings (eg, home and school).

A persistent pattern of excessive inattention (mostly girls) and/or hyperactivity/impulsivity (mostly boys); typically presents between ages 3 and 13. Often shows a familial pattern.

History/Pe

Diagnosis requires **five or more symptoms** from each category listed below for **6 or more months** in **at least two settings,** leading to significant social and academic impairment. Symptoms must be present in patients **before age 12.**

- **Inattention:** Exhibits a **poor attention span** in schoolwork/play; displays poor attention to detail or careless mistakes; has **difficulty following instructions or finishing tasks;** is forgetful and easily distracted.
- **Hyperactivity/impulsivity: Fidgets;** leaves seat in classroom; runs around inappropriately; cannot play quietly; talks excessively; **does not wait for his or her turn; interrupts others.**

Treatment

- Initial treatment may be nonpharmacologic (eg, behavior modification). Sugar and food additives are **not** considered etiologic factors.
- Pharmacologic treatment includes the following:
  - **Psychostimulants: Methylphenidate (Ritalin),** dextroamphetamine (Dexedrine), mixed salts of dextroamphetamine and amphetamine (Adderall). Adverse effects include insomnia, irritability, ↓ appetite, tic exacerbation, and ↓ growth velocity (normalizes when medication is stopped).
  - **Nonstimulants** (eg, SSRIs, nortriptyline, bupropion) and α_2**-agonists** (eg, **clonidine**), and atomoxetine (Strattera).

AUTISM SPECTRUM DISORDER

Persistent impairment in socialization, communication, and behavior. More common in males. Symptom severity and IQ vary widely. DSM 5 does not distinguish between the pervasive developmental disorders; severity is based on the level of support needed in the psychopathologic domains of social communication and restricted/repetitive behaviors.

KEY FACT

If you see ASD, think about associated congenital conditions such as Rett syndrome, tuberous sclerosis, and fragile X syndrome.

History/Pe

- Characterized by abnormal or **impaired social interaction and communication** together with **restricted activities and interests,** evident **before age 3.**
- Patients fail to develop normal social behaviors (eg, social smile, eye contact) and lack interest in relationships.
- Development of spoken language is delayed or absent.
- Children show **stereotyped speech and behavior** (eg, hand flapping) and restricted interests (eg, preoccupation with parts of objects).

Treatment

- Intensive special education, **behavioral management,** and symptom-targeted medications (eg, neuroleptics for aggression; SSRIs for stereotyped behavior).
- Family support and counseling are crucial.

DISRUPTIVE BEHAVIORAL DISORDERS

Include conduct disorder and oppositional defiant disorder. More common among men or boys and in patients with a history of abuse.

History/Pe

- **Oppositional defiant disorder:** A pattern of **negativistic, defiant, disobedient, and hostile behavior** toward authority figures (eg, losing one's temper, arguing) for 6 or more months. **May progress to conduct disorder.**
- **Conduct disorder:** A repetitive, persistent pattern of **violating the basic rights of others** or age-appropriate **societal norms or rules** for **1 year or more.** Behaviors may be aggressive (eg, rape, robbery, animal cruelty) or nonaggressive (eg, stealing, lying, deliberately annoying people). **May progress to antisocial personality disorder in adulthood.**

KEY FACT

Conduct disorder is seen in **C**hildren. **A**ntisocial personality disorder is seen in **A**dults.

Treatment

Individual and family therapy.

INTELLECTUAL DEVELOPMENTAL DISORDER

Associated with male gender, chromosomal abnormalities, congenital infections, teratogens (including alcohol/illicit substances), and inborn errors of metabolism.

History/Pe

- Patients have impaired intellectual functioning **(IQ < 70)** with **deficits in adaptive functioning** (eg, hygiene, social skills); onset is before age 18.
- Levels of severity are **mild (IQ 50–70; 85% of cases),** moderate **(IQ 35–49),** severe **(IQ 20–34),** and profound **(IQ < 20).**

KEY FACT

Fetal alcohol syndrome is the most common avoidable cause of intellectual disability.

Treatment

- 1° prevention consists of educating the general public about possible causes of intellectual disability and providing optimal prenatal screening to mothers.
- Treatment measures include family counseling and support; speech and language therapy; occupational/physical therapy; behavioral intervention; educational assistance; and social skills training.

TOURETTE SYNDROME

More common in men and boys; shows a genetic predisposition. **Associated with ADHD, learning disorders,** and **OCD.**

History/Pe

- Begins before age 18.
- Characterized by **multiple motor tics** (eg, blinking, grimacing) **and vocal tics** (eg, grunting, coprolalia) occurring many times per day, recurrently, for > 1 year with social or occupational impairment.

KEY FACT

Coprolalia = repetition of obscene words.

Treatment

- Treatment includes **dopamine receptor antagonists** (haloperidol, pimozide) or clonidine.
- Behavioral therapy may be of benefit, and counseling can aid in social adjustment and coping. Stimulants can worsen or precipitate tics.

Psychotic Disorders

SCHIZOPHRENIA

KEY FACT

Psychosis (hallucinations and/or delusions without insight) ≠ schizophrenia. Differential diagnosis must also include medical diseases, other psychiatric illnesses, and substance-induced psychosis.

KEY FACT

Terms used to describe components of psychosis:

- **Delusion:** A fixed false idiosyncratic belief.
- **Hallucination:** Perception without an existing external stimulus.
- **Illusion:** Misperception of an actual external stimulus.

Characterized by psychotic symptoms (hallucinations, bizarre delusions), disorganization (thought disorder, behavioral disturbances), and negative symptoms (poverty of affect, thought, and social interaction).

- **Epidemiology:** Prevalence is approximately 1%; men and women are affected equally. **Peak onset is earlier in men (ages 18–25)** than in **women (ages 25–35).** Schizophrenia in first-degree relatives also ↑ risk. Up to 50% of patients attempt suicide, and **10% of those affected successfully commit suicide.**
- **Etiology:** Etiologic theories focus on neurotransmitter abnormalities such as dopamine dysregulation (frontal hypoactivity and limbic hyperactivity) and brain abnormalities on CT and MRI (enlarged ventricles and ↓ cortical volume).

History/Pe

- Two or more of the following are present continuously for **6 or more months** with **social or occupational dysfunction:**
  - **Positive symptoms:** Hallucinations (most often auditory), delusions, disorganized speech, bizarre behavior, and thought disorder.
  - **Negative symptoms:** Flat affect, ↓ emotional reactivity, poverty of speech, lack of purposeful actions, and anhedonia.
- See Table 2.14-1 for the differential diagnosis of psychosis.

TABLE 2.14-1. Differential Diagnosis of Psychosis

Disorder	Duration/Characteristics
Psychotic disorders	**Brief psychotic disorder:** > 1 day and < 1 month. **Schizophreniform disorder:** > 1 month and < 6 months. Note: Both have same presentation as schizophrenia, but are usually preceded by stressors, have no prior episodes, are less likely to have negative symptoms, and have better lifetime prognosis. **Schizophrenia:** > 6 months. **Schizoaffective disorder:** Schizophrenia + major affective disorder (major depressive disorder or bipolar affective disorder).
Personality disorders	**Schizotypal:** "Magical thinking." **Schizoid:** "Loners."
Delusional disorder	Persistent **nonbizarre** fixed delusions without disorganized thought process, hallucinations, or negative symptoms of schizophrenia; subtypes are jealous, paranoid, somatic, erotomanic, or grandiose. **Day-to-day functioning mostly unaffected.**

Treatment

- **Antipsychotics** (see Table 2.14-2); **long-term follow-up.**
- Supportive psychotherapy, training in social skills, vocational rehabilitation, and illness education may help.
- Negative symptoms may be more difficult to treat than positive symptoms; atypical antipsychotics are drug of choice.

MNEMONIC

Evolution of EPS—

4 and A

4 hours: **A**cute dystonia.
4 days: **A**kinesia.
4 weeks: **A**kathisia.
4 months: Tardive dyskinesia (often permanent).

Anxiety Disorders

GENERALIZED ANXIETY DISORDER

Uncontrollable, excessive anxiety or worry about multiple activities or events that leads to significant impairment or distress. The male-to-female ratio is 1:2; clinical onset is usually in the early 20s.

TABLE 2.14-2. Antipsychotic Medications

Drug Class		Examples	Indications	Side Effects
Typical antipsychotics	High potency.	Haloperidol, fluphenazin .	Psychotic disorders, acute agitation, acute mania, Tourette syndrome. Thought to be more effective for positive symptoms of schizophrenia; primarily block D2 dopamine receptors. For patients in whom compliance is a major issue, consider antipsychotics that come in depot forms (eg, haloperidol, fluphenazine)	**EPS** (see Table 2.14-3) > anticholinergic symptoms (dry mouth, urinary retention, constipation). QTc prolongation and torsades, especially IV haloperidol. **Neuroleptic malignant syndrome** (see Table 2.14-3).
	Low potency.	Thioridazine, chlorpromazine.	Same as high potency.	**Anticholinergic** > EPS. More sedative. Greater risk of orthostatic hypotension. Thioridazine causes dose-dependent QTc prolongation and irreversible retinal pigmentation.
Atypical antipsychotics		Risperidone (also available in long-acting depot injection), quetiapine, olanzapine, ziprasidone, aripiprazole, clozapine.	Currently firs -line treatment for schizophrenia given fewer EPS and anticholinergic effects. Clozapine is reserved for severe treatment resistance and severe tardive dyskinesia.	Weight gain, type 2 diabetes mellitus, somnolence, sedation, and QTc prolongation. **Clozapine can cause agranulocytosis,** requiring weekly CBC monitoring during first 6 mo ths.

TABLE 2.14-3. EPS and Treatment

Subtype	Description	Time of Onset	Treatment
Acute dystonia	Prolonged, painful tonic muscle contraction or spasm (eg, torticollis, oculogyric crisis).	Hours	Anticholinergics (benztropine or diphenhydramine) are acute therapy; some patients on antipsychotics who are prone to dystonic reactions may need regular prophylactic dosing (eg, benztropine).
Dyskinesia	Pseudoparkinsonism (eg, shuffling gait, cogwheel rigidity).	Days	Give an anticholinergic (benztropine) or a dopamine agonist (amantadine). ↓ the dose of neuroleptic or discontinue (if tolerated).
Akathisia	Subjective/objective restlessness that is perceived as being distressing.	Weeks	↓ neuroleptic and try β-blockers (propranolol). Benzodiazepines or anticholinergics may help.
Tardive dyskinesia	Stereotypic, involuntary, painless oral-facial movements. Probably from dopamine receptor sensitization from chronic dopamine blockade. Often irreversible (50%).	Months	Discontinue or ↓ the dose of neuroleptic; attempt treatment with more appropriate drugs; and consider changing neuroleptic (eg, to clozapine or risperidone). **Giving anticholinergics or decreasing neuroleptics may initially worsen tardive dyskinesia.**
Neuroleptic malignant syndrome	Fever, muscle rigidity, autonomic instability, elevated CK and WBC, clouded consciousness.	Anytime	**Stop medication;** provide supportive care in the ICU; administer dantrolene or bromocriptine.

History/Pe

Presents with anxiety on most days **(6 or more months)** and with **three or more somatic symptoms** (restlessness, fatigue, difficulty concentrating, irritability, muscle tension, disturbed sleep).

Treatment

- **Short-term therapy:**
  - Benzodiazepines may be used for immediate symptom relief.
  - Taper benzodiazepines as soon as long-term treatment is established (eg, with SSRIs) in view of the high risk of tolerance and dependence.
  - Do not stop benzodiazepines "cold turkey," as patients may develop potentially lethal withdrawal symptoms similar to those of alcohol withdrawal.
- **Long-term therapy:**
  - Lifestyle changes.
  - Psychotherapy.
  - **Medications** (see Table 2.14-4): SSRIs (first-line treatment), venlafaxine, buspirone. Patient education is essential.

KEY FACT

Buspirone is another drug, in addition to SSRIs, that should not be used in conjunction with MAOIs.

PANIC DISORDER

Characterized by recurrent, unexpected panic attacks. Two to three times more common in women than in men. **Agoraphobia** is present in 30–50% of cases. The average age of onset is 25, but may occur at any age.

TABLE 2.14-4. Anxiolytic Medications

Drug Class	Indications	Side Effects
SSRIs (fluoxetine, sertraline, paroxetine, citalopram, escitalopram)	GAD, OCD, panic disorder.	Nausea, GI upset, somnolence, sexual dysfunction, agitation.
Buspirone	GAD, social phobia. **No tolerance, dependence, or withdrawal.**	Seizures with chronic use.
β-blockers	Phobic disorders (best when given prior to exposure).	Bradycardia, hypotension.
Benzodiazepines	Anxiety, insomnia, alcohol withdrawal, muscle spasm, night terrors, sleepwalking.	↓ sleep duration; risk of abuse, tolerance, and dependence; disinhibition in young or old patients; confusion.

History/Pe

- **Panic attacks** are defined as discrete **periods of intense fear or discomfort** in which at least four of the following symptoms develop abruptly and peak within 10 minutes: tachypnea, chest pain, **palpitations, diaphoresis,** nausea, trembling, dizziness, **fear of dying** or "going crazy," depersonalization, or hot flashes.
- Perioral and/or acral paresthesias, when present, are fairly specific to panic attacks, which produce hyperventilation and low O_2 saturation.
- Patients present with **1 or more months** of concern about having additional attacks or significant behavior change as a result of the attacks—eg, avoiding situations that may precipitate attacks.
- **Determine whether a patient has panic disorder with or without agoraphobia** so that agoraphobia can also be addressed in the treatment plan.

Treatment

- **Short-term therapy:** Benzodiazepines (eg, clonazepam) may be used for immediate relief, but long-term use should be avoided in light of the potential for addiction and tolerance (see Table 2.14-4). Taper benzodiazepines as soon as long-term treatment is initiated (eg, SSRIs).
- **Long-term therapy:**
  - CBT.
  - **Medications:** SSRIs (first-line therapy), TCAs.

PHOBIAS (SOCIAL AND SPECIFIC)

Distinguished as follows:

- **Social phobia:** Characterized by marked fear provoked by **social or performance situations** in which embarrassment may occur. It may be specific (eg, public speaking, urinating in public) or general (eg, social interaction) and often begins in adolescence.

KEY FACT

Walks like a chicken, talks like a chicken … it's a bear. Differential diagnosis for panic disorders:

- **Medical conditions:** Angina, MI, arrhythmias, hyperthyroidism, pheochromocytoma.
- **Psychiatric conditions:** Substance-induced anxiety, GAD, PTSD.

Q

A 26-year-old woman has been "hearing voices" and has isolated herself from her friends and family. Within the past 2 months, she has also been sleeping poorly and has reported feeling sad. What is her most likely diagnosis?

- **Specific phobia:** Anxiety is provoked by exposure to a **feared object or situation** (eg, animals, heights, airplanes). Most cases begin in childhood.

History/Pe

Presents with excessive or unreasonable fear and/or avoidance of an object or situation that is persistent and leads to significant distress or impairment in function. **Patients recognize that their fear is excessive.**

KEY FACT

Agoraphobia is defined as fear of being alone in public places. Literally translated, it means "fear of the marketplace."

Treatment

- **Specific phobias: CBT** involving desensitization through incremental exposure to the feared object or situation along with relaxation techniques. Other options include supportive, family, and insight-oriented psychotherapy.
- **Social phobias: CBT,** SSRIs, low-dose benzodiazepines, or β-blockers (for performance anxiety) may be used (see Table 2.14-4).

Obsessive-Compulsive Disorder and Related Disorders

OBSESSIVE-COMPULSIVE DISORDER

Characterized by obsessions and/or compulsions that lead to significant distress and dysfunction in social or personal areas. Typically presents in late adolescence or early adulthood; prevalence is equal in male and female patients. Often chronic and difficult to treat.

KEY FACT

Many OCD patients initially present to a nonpsychiatrist—eg, they may consult a dermatologist with a skin complaint 2° to overwashing hands.

History/Pe

- **Obsessions: Persistent, unwanted, and intrusive ideas, thoughts, impulses, or images** that lead to marked anxiety or distress (eg, fear of contamination, fear of harm to oneself or to loved ones).
- **Compulsions: Repeated mental acts or behaviors** that neutralize anxiety from obsessions (eg, handwashing, elaborate rituals for ordinary tasks, counting, excessive checking).
- Patients **recognize these behaviors as excessive and irrational products of their own minds** (vs obsessive-compulsive personality disorder, or OCPD; see Table 2.14-5).
- Patients wish they could get rid of the obsessions and/or compulsions.

TABLE 2.14-5. OCD vs OCPD

OCD	OCPD
Characterized by obsessions and/or compulsions.	Patients are excessively conscientious and inflexible.
Patients **recognize** the obsessions/compulsions and want to be rid of them (ego dystonic).	Patients **do not recognize** their behavior as problematic (ego syntonic).

A

Schizoaffective disorder causes symptoms of schizophrenia with mood symptoms, with at least 2 weeks when psychotic symptoms were present without any mood symptoms. Patients often have chronic psychotic symptoms, even after mood symptoms have resolved.

Treatment

- Pharmacotherapy (SSRIs are first-line pharmacologic treatment).
- CBT using exposure and desensitization relaxation techniques.
- Patient education is imperative.

BODY DYSMORPHIC DISORDER

Characterized by preoccupation with imagined or slight defects in physical appearance that are usually imperceptible to others, leading to significant distress/impairment. Actions and behaviors are obsessive and repetitive (ie, mirror checks, comparisons) in response to concerns of appearance.

Treatment

SSRIs.

Trauma and Stressor-Related Disorders

POSTTRAUMATIC STRESS DISORDER

Clinically significant stress or impairment in day-to-day social/work interactions as a result of direct exposure to an extreme, **life-threatening traumatic event** (eg, assault, combat, injury, rape, accident, violent crime), witnessing a traumatic event, indirect exposure through learning of a life-threatening event involving a close family member or friend, or reexposure to trauma-related events through occupation.

History/Pe

- Characterized by the following four symptom clusters:
  - **Intrusion: Reexperiencing of the event** through nightmares, flashbacks, intrusive memories.
  - **Avoidance** of stimuli associated with the trauma.
  - **Negative alterations in mood and cognitions: Numbed responsiveness** (eg, detachment, anhedonia), guilt, self-blame.
  - **Changes in arousal and reactivity: ↑ arousal** (eg, hypervigilance, exaggerated startle), sleep disturbances, aggression/irritability, and poor concentration that leads to significant distress or impairment in functioning.
- **Symptoms must persist for > 1 month;** the same symptoms present for 3 days to 1 month characterize acute stress disorder.

treatment

- **Short-term therapy:** To target anxiety; includes β-blockers and α_2-agonists (eg, clonidine).
- **Long-term therapy:**
  - **Medications:** SSRIs are first line; buspirone, TCAs, and MAOIs may be helpful. Benzodiazepines are also used but should be avoided in light of their addictive potential, as there is a high incidence of substance abuse among patients with PTSD.
  - **Psychotherapy** and **support groups** are useful.

KEY FACT

Top causes of PTSD in male patients are (1) sexual assault and (2) combat. Top causes of PTSD in female patients are (1) childhood abuse and (2) sexual assault.

KEY FACT

In patients with a history of substance abuse, benzodiazepines should be avoided in view of their high addictive potential.

ADJUSTMENT DISORDER

Clinically significant distress **following a profound life change (eg, divorce, unemployment, financial issues, romantic breakup),** not severe enough to meet criteria for another mental disorder.

History/Pe

Occurs within 3 months after onset of the stressor, can place person at higher risk for suicidality. Symptoms can be further characterized by **anxiety, depressed mood,** or **issues in conduct.** Usually resolves with 6 months of onset.

Treatment

No pharmacologic treatment! Treat adjustment disorder with supportive counseling.

Neurocognitive Disorders

Affect memory, orientation, judgment, and attention.

DEMENTIA (AKA MAJOR NEUROCOGNITIVE DISORDER)

A decline in **cognitive** functioning with **global deficits. Level of consciousness is stable (vs delirium).** Prevalence is highest among those > 85 years of age. The course is persistent and progressive. The most common causes are **Alzheimer disease** (65%) and **vascular dementia** (20%). Other causes are outlined in the mnemonic **DEMENTIASS.**

History/Pe

Diagnostic criteria include **memory impairment and one or more** of the following:

- **The four A's of dementia** (the progression of cognitive impairment follows this order): **A**mnesia (partial or total memory loss), **A**phasia (language impairment), **A**praxia (inability to perform motor activities), **A**gnosia (inability to recognize previously known objects/places/people).
- **Impaired executive function (problems with planning, organizing, and abstracting)** in the presence of a **clear sensorium.**
- Personality, mood, and behavior changes are common (eg, wandering and aggression).

Diagnosis

- A careful history and physical is critical. Serial mini-mental state exams should be performed.
- Rule out treatable causes of dementia; obtain CBC, RPR, CMP, TFTs, HIV, B_{12}/folate, ESR, UA, and a head CT or MRI.
- Table 2.14-6 outlines key characteristics distinguishing dementia from delirium.

Treatment

- Provide **environmental cues** and a rigid structure for the patient's daily life.

MNEMONIC

Causes of dementia—

DEMENTIASS

Degenerative diseases (Parkinson, Huntington)
Endocrine (thyroid, parathyroid, pituitary, adrenal)
Metabolic (alcohol, electrolytes, vitamin B_{12} deficiency, glucose, hepatic, renal, Wilson disease)
Exogenous (heavy metals, carbon monoxide, drugs)
Neoplasia
Trauma (subdural hematoma)
Infection (meningitis, encephalitis, endocarditis, syphilis, HIV, prion diseases, Lyme disease)
Affective disorders (pseudodementia)
Stroke/**S**tructure (vascular dementia, ischemia, vasculitis, normal-pressure hydrocephalus)

TABLE 2.14-6. Delirium vs Dementia

Variable	Delirium	Dementia
Level of attention	Impaired (fluctuating).	Usually alert.
Onset	Acute.	Gradual.
Course	Fluctuating from hour to hour, "sundowning."	Progressive deterioration.
Consciousness	Clouded.	Intact.
Hallucinations	Present (often visual or tactile).	Occur in approximately 30% of patients in highly advanced disease.
Prognosis	Reversible.	Largely irreversible, but up to 15% of cases are due to treatable causes and are reversible.
Treatment	Treat underlying causes. Low-dose antipsychotics; environmental changes (ie, low-stimulus environment, frequent orientation to day and time, shades up during daytime to reestablish circadian rhythm).	Cholinesterase inhibitors; low-dose antipsychotics (primarily for behavior disturbances). Environmental changes.

- **Cholinesterase inhibitors** are used to treat. Low-dose **antipsychotics** may be used for psychotic symptoms and sometimes for aggression, but with the added risk of cardiovascular events in elderly patients. **Avoid benzodiazepines,** which may exacerbate disinhibition and confusion.
- Family, caregiver, and patient education and support are imperative.

DELIRIUM

An acute **disturbance of consciousness** with **altered cognition** that develops over a short period of time (usually hours to days). Children, the elderly, and hospitalized patients (eg, **ICU psychosis**) are particularly susceptible. Major causes are outlined in the mnemonic **I WATCH DEATH.** Symptoms are potentially reversible if the underlying cause can be treated.

History/Pe

- Presents with acute onset of **waxing and waning consciousness** with lucid intervals and **perceptual disturbances** (hallucinations, illusions, delusions).
- Patients may be combative, anxious, paranoid, or stuporous.
- Also characterized by a ↓ attention span and short-term memory, a reversed sleep-wake cycle, and ↑ symptoms at night (sundowning).

MNEMONIC

Major causes of delirium—

I WATCH DEATH

Infection
Withdrawal
Acute metabolic/substance **A**buse
Trauma
CNS pathology
Hypoxia
Deficiencie
Endocrine
Acute vascular/MI
Toxins/drugs
Heavy metals

KEY FACT

It is common for delirium to be superimposed on dementia.

KEY FACT

MDEs can be present in major depressive disorder or in bipolar disorder types I and II.

MNEMONIC

Symptoms of a depressive episode—

SIG E CAPS

Sleep (hypersomnia or insomnia)
Interest (loss of interest or pleasure in activities)
Guilt (feelings of worthlessness or inappropriate guilt)
Energy (↓) or fatigue
Concentration (↓)
Appetite (↑ or ↓) or weight (↑ or ↓)
Psychomotor agitation or retardation
Suicidal ideation

MNEMONIC

TCA toxicity—

Tri-C's

Convulsions
Coma
Cardiac arrhythmias

Diagnosis

- Check vital signs, utilize pulse oximetry, and provide glucose; perform physical and neurologic examinations.
- Note recent medications (narcotics, anticholinergics, steroids, or benzodiazepines), substance use, prior episodes, medical problems, signs of organ failure (kidney, liver), and infection (**occult UTI is common in the elderly;** check UA).
- Order lab and radiologic studies to identify a possible underlying cause.

Treatment

- **Treat underlying causes** (delirium is often reversible).
- Normalize fluids and electrolytes.
- **Optimize the sensory environment, and provide necessary visual and hearing aids.**
- Use low-dose **antipsychotics** (eg, haloperidol) for agitation and psychotic symptoms.
- Conservative use of **physical restraints** may be necessary to prevent harm to the patient or others.

Mood Disorders

Also known as **affective disorders.**

MAJOR DEPRESSIVE DISORDER

A mood disorder characterized by one or more major depressive episodes (MDEs). The male-to-female ratio is 1:2; lifetime prevalence ranges from 15% to 25%. **Onset is usually in the mid-20s;** in the elderly, prevalence ↑ with age. Chronic illness and stress ↑ risk. Approximately 2–9% of patients die by suicide.

History/PE

Diagnosis requires **depressed mood or anhedonia (loss of interest/pleasure) and five or more signs/symptoms** from the **SIG E CAPS** mnemonic for a **2-week period** (you should be sure to learn this mnemonic to ace the MDD questions). Table 2.14-7 outlines the differential diagnosis of conditions that can be mistaken for depression. Selected depression subtypes include the following:

- **Psychotic features:** Typically **mood-congruent** delusions/hallucinations.
- **Postpartum:** Occurs **within 1 month postpartum;** has a 10% incidence and a high risk of recurrence. Psychotic symptoms are common (see Table 2.14-8).
- **Atypical:** Characterized by weight gain, hypersomnia, and rejection sensitivity.
- **Seasonal:** Depressive episodes tend to occur during a particular season, most commonly winter. Responds well to light therapy with or without antidepressants.
- **Double depression:** Major depressive episode (MDE) in a patient with dysthymia. Has a poorer prognosis than MDE alone.

Treatment

- **Pharmacotherapy:**
  - Effective in 50–70% of patients.
  - Allow 2–6 weeks to take effect; treat for 6 or more months (see Table 2.14-9).

TABLE 2.14-7. Differential Diagnosis of Major Depression

Disorder	Description and Examples
Mood disorder due to a medical condition	Hypothyroidism, Parkinson disease, CNS neoplasm, other neoplasms (eg, pancreatic cancer), stroke (especially ACA stroke), dementias, parathyroid disorders.
Substance-induced mood disorder	Illicit drugs, alcohol, antihypertensives, corticosteroids, OCPs.
Adjustment disorder with depressed mood	A constellation of symptoms that resemble an MDE but do not meet the criteria for MDE. Occurs within 3 months of an identifiable stressor.
Normal bereavement	Occurs after the loss of a loved one. Involves no severe impairment/suicidality. Usually lasts < 6 months; should resolve within 1 year. May lead to MDD that requires treatment. Illusions/hallucinations of the deceased can be normal as long as the person recognizes them as such.
Dysthymia	Milder, chronic depression with depressed mood present most of the time for at least 2 years; often resistant to treatment.

- **Psychotherapy: Psychotherapy combined with antidepressants is more effective than either treatment alone.**
- **Electroconvulsive therapy (ECT):**
  - Safe, highly effective, and often lifesaving therapy that is reserved for refractory depression or psychotic depression, if rapid improvement in mood is needed (severe suicidality), or intractable mania and psychosis. Also safe during pregnancy.
  - Usually requires two to three times per week treatment for a total of 6–12 treatments.
  - Adverse effects include postictal confusion, arrhythmias, headache, and **anterograde amnesia.**
  - No absolute contraindications. Relative contraindications include recent MI/stroke, intracranial mass, and high anesthetic risk.

TABLE 2.14-8. Differential Diagnosis of Postpartum Disorders

Subtype	Time of Onset	Symptoms
Postpartum "blues"	Within 2 weeks of delivery.	Sadness, moodiness, emotional lability. No thoughts about hurting baby.
Postpartum psychosis	2–3 weeks postdelivery.	Delusions and depression. May have thoughts about hurting baby.
Postpartum depression	1–3 months postdelivery.	Same as above plus sleep disturbances and anxiety. Thoughts about hurting baby.

KEY FACT

Discontinue SSRIs at least 2 weeks before starting an MAOI. Wait 5 weeks if the patient was on fluoxetine.

Q

A 23-year-old woman complains of difficulty falling asleep and worsening anxiety that began 2 months earlier, after she was involved in a minor biking accident (bike vs car) in which she did not suffer any injuries. Since the accident, she has refused to participate in any outdoor activities. What is her most likely diagnosis?

TABLE 2.14-9. Indications and Side Effects of Common Antidepressants

Drug Class	Examples	Indications	Side Effects
SSRIs	Fluoxetine, sertraline, paroxetine, citalopram, fluvoxamine.	Depression, anxiety.	Sexual side effects, GI distress, agitation, insomnia, tremor, diarrhea. **Serotonin syndrome** (fever, myoclonus, mental status changes, cardiovascular collapse) can occur if SSRIs are used with MAOIs, illicit drugs, or herbal medications. Paroxetine can cause pulmonary hypertension in the fetus. Avoid in pregnancy.
Atypicals	Bupropion, mirtazapine, trazodone.	Depression, anxiety.	**Bupropion:** ↓ seizure threshold; minimal sexual side effects. Contraindicated in patients with eating disorders as well as in seizure patients. **Mirtazapine:** Weight gain, sedation. **Trazodone:** Highly sedating; priapism.
SNRIs	Venlafaxine, duloxetine.	Depression, anxiety, chronic pain.	**Venlafaxine:** Diastolic hypertension.
TCAs	Nortriptyline, desipramine, amitriptyline, imipramine.	Depression, anxiety disorder, chronic pain, migraine headaches, enuresis (imipramine).	Lethal with overdose resulting from cardiac conduction arrhythmias (eg, prolonged conduction through the AV node, long QRS). Monitor in the ICU for 3–4 days following an overdose. Anticholinergic effects (dry mouth, constipation, urinary retention, sedation).
MAOIs	Phenelzine, tranylcypromine, selegiline (a patch form is available).	Depression, especially atypical.	Hypertensive crisis if taken with high-tyramine foods (aged cheese, red wine). Sexual side effects, orthostatic hypotension, weight gain.

KEY FACT

SIG E CAPS = MDD. **DIG FAST** = BPD.

- **Phototherapy:** Effective for patients whose depression has a seasonal pattern.
- **Transcranial magnetic stimulation (TMS):** Now approved for the treatment of major depression. TMS is about as effective as medications for some patients but is not as effective as ECT.

BIPOLAR DISORDER

Prevalence is approximately 1% for type I and an additional 3% for type II; male and female patients are affected equally. A family history of bipolar illness significantly ↑ risk. The average age of onset is 20, and the frequency of mood episodes tends to ↑ with age. Up to 10–15% of those affected die by suicide. Subtypes are as follows:

- **Bipolar I:** Involves **at least one manic or mixed episode** (usually requiring hospitalization).
- **Bipolar II:** Involves **at least one MDE and one hypomanic episode** (less intense than mania). Patients do not meet the criteria for full manic or mixed episodes. Characterized predominantly by depression with occasional hypomanic episodes.
- **Rapid cycling:** Involves four or more episodes (MDE, manic, mixed, or hypomanic) in 1 year.
- **Cyclothymic:** Chronic and less severe, with alternating periods of hypomania and moderate depression for > 2 years.

A

Adjustment disorder, which consists of emotional and behavioral symptoms that develop in response to an identifiable stressor, lasts > 1 month and < 6 months, and does not have five or more symptoms of MDD.

History/Pe

- The mnemonic **DIG FAST** outlines the clinical presentation of mania.
- Patients may report excessive engagement in pleasurable activities (eg, excessive spending or sexual activity), reckless behaviors, and/or psychotic features.
- **Antidepressant use without a mood stabilizer may trigger manic episodes.**

Diagnosis

- A manic episode is **1 week or more of persistently elevated, expansive, or irritable mood** plus **three DIG FAST symptoms. Psychotic symptoms** are common in mania.
- Symptoms are not due to a substance or medical condition and lead to significant impairment socially, occupationally, or familially.
- Hypomania is similar but does not involve marked functional impairment or psychotic symptoms and does not require hospitalization.

Treatment

- **Bipolar mania:** Mania is considered a psychiatric emergency because of the impaired judgment and great risk of harm to self and others.
  - **Acute therapy:** Antipsychotics, lithium, valproate.
  - **Maintenance therapy:** Mood stabilizers (see Table 2.14-10).
  - Use benzodiazepines for refractory agitation.
- **Bipolar depression:** Mood stabilizers with or without antidepressants. **Start mood stabilizers first** (see Table 2.14-10) to avoid inducing mania. ECT may be used to treat refractory cases.

MNEMONIC

Symptoms of mania—

DIG FAST

Distractibility
Insomnia (↓ need for sleep)
Grandiosity (↑ self-esteem)/more **G**oal directed
Flight of ideas (or racing thoughts)
Activities/psychomotor **A**gitation
Sexual indiscretions/other pleasurable activities
Talkativeness/pressured speech

TABLE 2.14-10. Mood Stabilizers

Drug Class	Indications	Side Effects
Lithium	First-line mood stabilizer. Used for acute mania (in combination with antipsychotics), for prophylaxis in BPD, and for augmentation in depression treatment. Also decreases suicide risk.	Thirst, polyuria, diabetes insipidus, tremor, weight gain, hypothyroidism, nausea, diarrhea, seizures, teratogenicity (if used in the first trimester, 0.1% risk of Ebstein anomaly), acne, vomiting. Narrow therapeutic window (but blood level can be monitored). Lithium toxicity: blood level > 1.5 mEq/L; presents with ataxia, dysarthria, delirium, and acute renal failure. Avoid lithium in patients with ↓ renal function.
Carbamazepine	Second-line mood stabilizer; anticonvulsant; trigeminal neuralgia.	Nausea, skin rash, leukopenia, AV block. Teratogenicity (0.5–1% neural tube defect). Rarely, aplastic anemia (monitor CBC biweekly). SJS.
Valproic acid	BPD; anticonvulsant.	GI side effects (nausea, vomiting), tremor, sedation, alopecia, weight gain, teratogenicity (3–5% risk of neural tube defect). Rarely, pancreatitis, thrombocytopenia, fatal hepatotoxicity, and agranulocytosis.
Lamotrigine	Second-line mood stabilizer; anticonvulsant.	Blurred vision, GI distress, SJS. ↑ dose slowly to monitor for rashes.

MNEMONIC

Characteristics of personality disorders—

MEDIC

Maladaptive
Enduring
Deviate from cultural norms
Infl xible
Cause impairment in social or occupational functioning

- In patients with **severe depression or bipolar II with predominantly depressive features,** antidepressant treatment can be augmented with low-dose lithium—eg, at blood levels of 0.4–0.6 mEq/L.

Personality Disorders

Personality can be defined as an individual's set of emotional and behavioral traits, which are generally stable and predictable. Personality disorders are defined when one's traits become chronically rigid and maladaptive, and affect most aspects of one's life (see the mnemonic **MEDIC**). Onset occurs by early adulthood. Specific disorders are outlined in Table 2.14-11.

TABLE 2.14-11. Signs and Symptoms of Personality Disorders

Disorder	Characteristics	Clinical Presentation
	Cluster A: "Weird"	
Paranoid	Distrustful, suspicious; interpret others' motives as malevolent.	59-year-old man who lives alone constantly feels that his neighbor's children are spying on him and plotting to break into his home. He has installed security cameras all around his property to obtain proof. He feels he cannot trust the police to do a good job because they will probably take the side of his neighbors.
Schizoid	Isolated, detached "loners." Restricted emotional expression.	66-year-old man who moves to Thailand alone after retirement, has no desire to remain in contact with his family, and is very distant in his interactions. He stays in his remote accommodations without unnecessary travel and does not crave interaction with the locals.
Schizotypal	Odd behavior, perceptions, and appearance. **Magical thinking;** ideas of reference. Note: These patients may have eccentric/disorganized thoughts and behavior; however, they lack delusions and hallucinations that would classify them as schizophrenic.	35-year-old man with very strange ideas regarding the importance of crystals and their effect on health. He meticulously mines and collects crystals, feeling that they will one day prevent him from acquiring cancer.
	Cluster B: "Wild"	
Borderline	Unstable mood, relationships, and self-image; feelings of emptiness. Impulsive. History of suicidal ideation or self-harm. Note: These patients will use **splitting** as a defense mechanism.	28-year-old woman presents to clinic after having praised her new clinician as better than all the others. She reveals that she fi ed her last therapist, as he was not really helping. You notice she has fresh cuts in a row on her forearm.
Histrionic	Excessively emotional and attention seeking. Sexually provocative; theatrical.	35-year-old woman presents to clinic wearing a very low-cut blouse, adjusting her position to draw attention to herself. When she does not get attention, she breaks into tears, saying that no one notices her, not even her friends.

(continues)

TABLE 2.14-11. Signs and Symptoms of Personality Disorders (continued)

Disorder	Characteristics	Clinical Presentation
	Cluster B: "Wild"	
Narcissistic	Grandiose; need admiration; have sense of entitlement. Lack empathy.	45-year-old man sits impatiently tapping his foot in the waiting room of your office. He approaches the receptionist, demands to know where the doctor is, and tells her that he will have her fired and the doctor reported if he is not seen shortly. You are all wasting his time.
Antisocial	Violate rights of others, social norms, and laws. Impulsive; lack remorse. **Must have a prior diagnosis of conduct disorder.**	22-year-old man who was in juvenile detention for theft as a teenager and presents to your office now via court order after a brutal assault. He says that he doesn't need to be seen by a shrink and that the victim offended him and deserved the assault.
	Cluster C: "Worried and Wimpy"	
Obsessive-compulsive	Preoccupied with perfectionism, order, and control at the expense of efficiency. Inflexible morals and values. Note: Remember, in contrast to OCD, these patients don't feel their behavior is problematic.	35-year-old woman presents to your office at the request of her boss, who feels she is too focused on minute details on team projects and doesn't allow others to participate for fear of unwanted errors. She doesn't see anything wrong with this style of work, as she believes her coworkers can't be trusted to pay adequate attention to detail.
Avoidant	Socially inhibited; rejection sensitive. **Fear of being disliked or ridiculed, yet desires to have friends and social interactions.**	33-year-old man stays at home to avoid an office Christmas party, as he fears having to make small talk. He wants to go, though is more afraid that he will be inadequate or rejected by others.
Dependent	Submissive, clingy; have a need to be taken care of. Have difficulty making decisions. Feel helpless.	30-year-old woman presents to your office in crisis, saying that her parents just kicked her out of their house and she is struggling to survive on her own. She says she is too weak to even make choices at the grocery, as her mother would always care for her and now these decisions are overwhelming. She has been sitting outside of their house daily, hoping they will let her live there again.

Diagnosis

- Ask about attitudes, mood variability, activities, and reaction to stress.
- Patients have chronic problems dealing with responsibilities, roles, and stressors. They may also deny their behavior, have difficulty changing their behavior patterns, and frequently refuse psychiatric care.

Treatment

- **Psychotherapy** is the mainstay of therapy.
- **Pharmacotherapy** is reserved for cases with comorbid mood, anxiety, or psychotic signs/symptoms.

Q

A 22-year-old man frequently washes his hands, refuses to sit on chairs in public places, and will not use public transportation for fear of contracting diseases. He does not think his behaviors are abnormal, nor does he think his behaviors interfere with his daily activities. What is the diagnosis?

Substance Use Disorders

Substance use disorder is a maladaptive pattern of substance use that leads to clinically significant impairment. It can be applied to most substances of abuse, except caffeine. The patient must meet 2 of the 11 criteria within a 1-year period for diagnosis. The criteria can be grouped into four categories of symptoms and are as follows:

- Impaired control:
  - Consumption of greater amounts of the substance than intended.
  - Failed attempts to cut down use or abstain from the substance.
  - Increased amount of time spent acquiring, using, or recovering from effects.
  - Craving.
- Social impairment:
  - **Failure to fulfill responsibilities** at work, school, or home.
  - Continued substance use despite recurrent social or interpersonal problems 2° to the effects of such use (eg, frequent arguments with spouse over the substance use).
  - **Isolation** from life activities.
- Risky use:
  - Use of substances in **physically hazardous** situations (eg, driving while intoxicated).
  - Continued substance abuse despite recurrent physical or psychological problems 2° to the effect of the substance use.
- Pharmacologic:
  - **Tolerance** and use of progressively larger amounts to obtain the same desired effect.
  - **Withdrawal** symptoms when not taking the substance.

Note: Tolerance and withdrawal are not needed to make the diagnosis.

KEY FACT

Pinpoint pupils are not always a reliable sign of opioid ingestion, because coingestions can lead to normal or enlarged pupils. Also look for a ↓ respiratory rate, track marks, and ↓ breath sounds.

Diagnosis/Treatment

- Substance use is often denied or underreported, so seek out collateral information from family and friends.
- Severity is determined by number of symptoms present: mild, two to three; moderate, four to five; severe, more than six.
- Check urine and blood toxicology screens, LFTs, and serum EtOH level.
- The management of intoxication for selected drugs is described in Table 2.14-12.

ALCOHOL USE DISORDER

Occurs more often in **men** (4:1) and in those 21–34 years of age, although the incidence in women is rising. Also associated with a ⊕ family history.

A

This person suffers from obsessive-compulsive personality disorder (OCPD). These patients are perfectionists, are preoccupied with rules and order, and are often inflexible. Unlike patients with obsessive-compulsive disorder, those with OCPD typically are not disturbed by their disease.

History/Pe

See Table 2.14-12 for the symptoms of intoxication and withdrawal. Look for palmar erythema or telangiectasias as well as for other signs and symptoms of end-organ complications.

Diagnosis

Screen with the **CAGE questionnaire.** Monitor vital signs for evidence of withdrawal. Labs may reveal ↑ LFTs, LDH, and mean corpuscular volume.

TABLE 2.14-12. Signs and Symptoms of Substance Abuse

Drug	Intoxication	Withdrawal
Alcohol	Disinhibition, emotional lability, slurred speech, ataxia, aggression, blackouts, hallucinations, memory impairment, impaired judgment, coma.	Tremor, tachycardia, hypertension, malaise, nausea, seizures, DTs, agitation.
Opioids	Euphoria leading to apathy, CNS depression, constipation, **pupillary constriction,** and respiratory depression (life-threatening in overdose). Naloxone and naltrexone block opioid receptors and reverse effects, but beware of the antagonist clearing before the opioids, particularly with long-acting opioids such as methadone.	Dysphoria, insomnia, anorexia, myalgias, fever, lacrimation, diaphoresis, dilated pupils, rhinorrhea, piloerection, nausea, vomiting, stomach cramps, diarrhea, yawning. Opioid withdrawal is not life-threatening, "hurts all over," and does not cause seizures.
Amphetamines	Psychomotor agitation, impaired judgment, hypertension, **pupillary dilation,** tachycardia, fever, diaphoresis, anxiety, angina, euphoria, prolonged wakefulness/attention, arrhythmias, delusions, seizures, hallucinations. Haloperidol can be given for severe agitation and symptom-targeted medications (eg, antiemetics, NSAIDs).	Postuse "crash" with anxiety, lethargy, headache, stomach cramps, hunger, fatigue, depression/dysphoria, sleep disturbance, nightmares.
Cocaine	Psychomotor agitation, euphoria, impaired judgment, tachycardia, **pupillary dilation,** hypertension, paranoia, hallucinations, "cocaine bugs" (the feeling of bugs crawling under one's skin), sudden death. ECG changes from ischemia are often seen ("cocaine chest pain"). Treat with haloperidol for severe agitation along with symptom-specific medic tions (eg, to control hypertension).	Postuse "crash" with hypersomnolence, depression, malaise, severe craving, angina, suicidality, ↑ appetite, nightmares.
Phencyclidine hydrochloride (PCP)	**Assaultiveness,** belligerence, psychosis, violence, impulsiveness, psychomotor agitation, fever, tachycardia, **vertical/horizontal nystagmus,** hypertension, impaired judgment, ataxia, seizures, delirium. Give benzodiazepines or haloperidol for severe symptoms; otherwise reassure. Acidific tion of urine or gastric lavage can help eliminate the drug.	Recurrence of intoxication symptoms due to reabsorption in the GI tract; sudden onset of severe, random violence.
LSD	Marked anxiety or depression, delusions, visual hallucinations, flashback , pupillary dilation, impaired judgment, diaphoresis, tachycardia, hypertension, heightened senses (eg, colors become more intense). Supportive counseling; traditional antipsychotics for psychotic symptoms; benzodiazepines for anxiety.	None.
Marijuana	Euphoria, slowed sense of time, impaired judgment, social withdrawal, ↑ appetite, dry mouth, conjunctival injection, hallucinations, anxiety, paranoia, amotivational syndrome.	None.

(continues)

TABLE 2.14-12. Signs and Symptoms of Substance Abuse (continued)

Drug	Intoxication	Withdrawal
Barbiturates	Low safety margin; respiratory depression.	Anxiety, seizures, delirium, life-threatening cardiovascular collapse.
Benzodiazepines	Interactions with alcohol, amnesia, ataxia, somnolence, mild respiratory depression. (Avoid using for insomnia in the elderly; can cause paradoxic agitation even in relatively low doses.)	Rebound anxiety, seizures, tremor, insomnia, hypertension, tachycardia, death.
Caffeine	Restlessness, insomnia, diuresis, muscle twitching, arrhythmias, tachycardia, flushed fa e, psychomotor agitation.	Headache, lethargy, depression, weight gain, irritability, craving.
Nicotine	Restlessness, insomnia, anxiety, arrhythmias.	Irritability, headache, anxiety, weight gain, craving, bradycardia, difficu y concentrating, insomnia.

MNEMONIC

CAGE questionnaire:

1. Have you ever felt the need to **C**ut down on your drinking?
2. Have you ever felt **A**nnoyed by criticism of your drinking?
3. Have you ever felt **G**uilty about drinking?
4. Have you ever had to take a morning **E**ye opener?

More than one "yes" answer makes alcoholism likely.

Treatment

- Rule out medical complications; correct electrolyte abnormalities.
- Start a **benzodiazepine taper** for withdrawal symptoms. Add haloperidol for hallucinations and psychotic symptoms.
- Give **multivitamins and folic acid; administer thiamine before glucose** (which depletes thiamine) to prevent Wernicke encephalopathy.
- Give anticonvulsants to patients with a seizure history.
- Group therapy, disulfiram, or naltrexone can aid patients with dependence.
- Long-term rehabilitative therapy (eg, Alcoholic Anonymous).

Complications

- **GI bleeding from gastritis, ulcers, varices, or Mallory-Weiss tears.**
- **Pancreatitis, liver disease,** DTs, alcoholic hallucinosis, peripheral neuropathy, Wernicke encephalopathy, Korsakoff psychosis, fetal alcohol syndrome, cardiomyopathy, anemia, aspiration pneumonia, ↑ risk of sustaining trauma (eg, subdural hematoma).

Eating Disorders

ANOREXIA NERVOSA

Risk factors include female gender, low self-esteem, and high socioeconomic status. Also associated with OCD, MDD, anxiety, and careers/hobbies such as modeling, gymnastics, ballet, and running.

History/Pe

- Patients **restrict** (eg, severely restricting caloric intake by fasting or by excessively exercising) or **binge and purge** (through vomiting, laxatives, and diuretics).
- Signs and symptoms include cachexia, a body mass index (BMI) < 18, **lanugo,** dry skin, bradycardia, lethargy, hypotension, cold intolerance, and hypothermia (as low as 35°C [95°F]).
- See Table 2.14-13.

TABLE 2.14-13. Anorexia vs Bulimia

Variable	Anorexia nervosa	Bulimia nervosa
Presentation	Persistent restriction of caloric intake resulting in low body weight, an intense fear of weight gain, a distorted body image (patients perceive themselves as fat).	For at least once a week for 3 or more months, patients have episodes of binge eating and compensatory behaviors that include purging or fasting.
Weight	**Patients are underweight** (≥ 15% below expected weight).	Patients are of normal weight or are overweight.
Attitude toward illness	Patients are typically not distressed by their illness and may thus be resistant to treatment.	Patients are typically distressed about their symptoms and are thus easier to treat.
Treatment	Monitor calorie intake and weight gain; hospitalize if necessary. Psychotherapy. Treat comorbidities.	Psychotherapy ± antidepressants.

Diagnosis

Measure height and weight; check BMI; check **CBC, electrolytes,** endocrine levels, and **ECG.** Perform a **psychiatric evaluation** to screen patients for comorbid conditions.

Treatment

See Table 2.14-13.

Complications

- See Table 2.14-14.
- Mortality from **suicide** or medical complications is > **10%**

KEY FACT

There are two types of anorexia nervosa:

- Restricting type
- Binging/purge-eating type

TABLE 2.14-14. Medical Complications of Eating Disorders

Constitutional	Cardiac	GI	GU	Other
Cachexia Hypothermia Fatigue Electrolyte abnormalities (hypokalemia, pH abnormalities)	Arrhythmias Sudden death Hypotension Bradycardia Prolonged QT interval	Dental erosions and decay Abdominal pain Delayed gastric emptying	Amenorrhea Nephrolithiasis	**Dermatologic:** Lanugo **Hematologic:** Leukopenia **Neurologic:** Seizures **Musculoskeletal:** Osteoporosis, stress fractures

KEY FACT

Bulimic patients tend to be more disturbed by their behavior than anorexics and are more easily engaged in therapy. Anorexic patients deny health risks associated with their behavior, making them resistant to treatment.

KEY FACT

Bupropion should be avoided in the treatment of patients with eating disorders, as it is associated with a ↓ seizure threshold.

BULIMIA NERVOSA

More common among women; associated with low self-esteem, mood disorders, and OCD.

History/Pe

- **See Table 2.14-13.**
- **Signs** include **dental enamel erosion, enlarged parotid glands,** and **scars on the dorsal hand surfaces** (if there is a history of repeated induced vomiting).

Treatment

See Table 2.14-13.

Complications

See Table 2.14-14.

Miscellaneous Disorders

SEXUAL DISORDERS

Sexual Changes With Aging

- Interest in sexual activity usually does not ↓ with aging.
- Men usually require ↑ stimulation of the genitalia for longer periods of time to reach orgasm; intensity of orgasm ↓, and the length of the refractory period before the next orgasm ↑.
- In women, estrogen levels ↓ after menopause, leading to vaginal dryness and thinning, which may result in discomfort during coitus. May be treated with hormone replacement therapy, estrogen vaginal suppositories, or other vaginal creams.

Paraphilic Disorders

Preoccupation with or engagement in unusual sexual fantasies, urges, or behaviors for > 6 months with clinically significant impairment in one's life. There are eight classified disorders, characterized by disordered courtship (voyeurism, exhibitionism, and frotteurism), disordered preferences (pedophilia, transvestic fetishism, fetishism), and pleasure in inflicting/receiving pain (sadism, masochism). See Table 2.14-15.

Treatment includes insight-oriented psychotherapy and behavioral therapy. Antiandrogens (eg, Depo-Provera) have been used for hypersexual paraphilic activity.

Gender Dysphoria

- **Strong, persistent cross-gender identification** and **discomfort with one's assigned sex or gender role of the assigned sex** in the absence of intersexual disorders. Patients may have a history of dressing like the opposite sex, taking sex hormones, or pursuing surgeries to reassign their sex.
- More common in men than in women. Associated with depression, anxiety, substance abuse, and personality disorders.
- **Tx:** Treatment is complex and includes educating the patient about culturally acceptable behavior patterns and addressing comorbidities. Other

TABLE 2.14-15. Features of Common Paraphilic Disorders

Disorder	Clinical Manifestations
Exhibitionistic	Sexual arousal from exposing one's genitals to a stranger.
Pedophilic	Urges or behaviors involving sexual activities with children.
Voyeuristic	Observing unsuspecting persons unclothed or involved in sex.
Fetishistic	Use of nonliving objects (often clothing) for sexual arousal.
Transvestic	Cross-dressing for sexual arousal.
Frotteuristic	Touching or rubbing one's genitalia against a nonconsenting person (common in subways).
Sexual sadism	Sexual arousal from inflicting suffering on sexual partner.
Sexual masochism	Sexual arousal from being hurt, humiliated, bound, or threatened.

options include sex-reassignment surgery or hormonal treatment (eg, estrogen for men, testosterone for women). Supportive psychotherapy is helpful.

Sexual Dysfunction

- Problems in sexual **arousal, desire, or orgasm,** or **pain** with sexual intercourse.
- Prevalence is 30%; one-third of cases are attributable to biologic factors and another third to psychological factors.
- **Tx:** Treatment depends on the particular condition. Pharmacologic strategies include sildenafil (Viagra) and bupropion (Wellbutrin). Psychotherapeutic strategies include sensate focusing.

SLEEP DISORDERS

Up to one-third of all American adults suffer from some type of sleep disorder during their lives. The term dyssomnia describes any condition that leads to a disturbance in the normal rhythm or pattern of sleep. Insomnia is the most common example. **Risk factors** include female gender, the presence of mental and medical disorders, substance abuse, and advanced age.

1° Insomnia

- **Affects up to 30% of the general population;** causes sleep disturbance that is not attributable to physical or mental conditions. Often exacerbated by anxiety, and patients may become preoccupied with getting enough sleep.
- **Dx:** Patients present with a history of **nonrestorative sleep** or **difficulty initiating or maintaining sleep** that is present at least three times per week for 1 month.
- **Tx:**
  - First-line therapy includes the initiation of **good sleep hygiene** measures.
  - Pharmacotherapy is considered second-line therapy and should be **initiated with care for short periods of time** (< 2 weeks). Pharmacologic

KEY FACT

Recommended sleep hygiene measures: Stimulus control therapy to reestablish a circadian (24-hour) sleep/wake cycle.

- Establishment of a regular sleep schedule
- Limiting of caffeine intake
- Avoidance of daytime naps
- Warm baths in the evening
- Use of the bedroom for sleep and sexual activity only
- Exercising early in the day
- Relaxation techniques
- Avoidance of large meals near bedtime

agents include diphenhydramine (Benadryl), zolpidem (Ambien), zaleplon (Sonata), and trazodone (Desyrel).

1° Hypersomnia

- **Dx:** Diagnosed when a patient complains of **excessive daytime sleepiness or nighttime sleep** that occurs for > 1 month. The excessive somnolence cannot be attributable to medical or mental illness, medications, poor sleep hygiene, insufficient sleep, or narcolepsy.
- **Tx:**
  - First-line therapy includes **stimulant drugs** such as amphetamines.
  - Antidepressants such as SSRIs may be useful in some patients.

Narcolepsy

- May affect up to 0.16% of the population. Onset typically occurs by young adulthood, generally before age 30. Some forms of narcolepsy may have a genetic component.
- **Dx:**
  - Manifestations include **excessive daytime somnolence** and ↓ **REM sleep latency** on a daily basis for at least 3 months. **Sleep attacks** are the classic symptom; patients cannot avoid falling asleep.
  - The characteristic excessive sleepiness may be associated with the following:
    - **Cataplexy:** Sudden loss of muscle tone that leads to collapse.
    - **Hypnagogic hallucinations:** Occur as the patient is falling asleep.
    - **Hypnopompic hallucinations:** Occur as the patient awakens.
    - **Sleep paralysis:** Brief paralysis upon awakening.
- **Tx:** Treat with a regimen of **scheduled daily naps** plus **stimulant drugs** such as amphetamines; give SSRIs for cataplexy.

Sleep Apnea

- Occurs 2° to **disturbances in breathing** during sleep that lead to **excessive daytime somnolence** and **sleep disruption.** Etiologies can be either central or peripheral.
  - **Central sleep apnea (CSA):** A condition in which both airflow and respiratory effort cease. CSA is linked to **morning headaches,** mood changes, and repeated awakenings during the night.
  - **Obstructive sleep apnea (OSA):** A condition in which airflow ceases as a result of obstruction along the respiratory passages. OSA is strongly associated with **snoring.** Risk factors include **male gender, obesity,** prior upper airway surgeries, a deviated nasal septum, a large uvula or tongue, and retrognathia (recession of the mandible).
- In both forms, arousal results in cessation of the apneic event.
- Associated with **sudden death in infants and the elderly,** headaches, depression, ↑ systolic BP, and **pulmonary hypertension.**
- **Dx: Sleep studies (polysomnography)** document the number of arousals, obstructions, and episodes of ↓ O_2 saturation; distinguish OSA from CSA; and identify possible movement disorders, seizures, or other sleep disorders.
- **Tx:**
  - **OSA:** Nasal continuous positive airway pressure (CPAP). Weight loss if obese. In children, most cases are due to tonsillar/adenoidal hypertrophy, which is corrected surgically.
  - **CSA:** Mechanical ventilation (eg, BiPAP) with a backup rate for severe cases.

Circadian Rhythm Sleep Disorder

- A spectrum of disorders characterized by a **misalignment between desired and actual sleep** periods. Subtypes include jet-lag type, shift-work type, delayed sleep-phase type, and unspecified.
- **Tx:**
  - The jet-lag type usually **resolves** within 2–7 days **without specific treatment.**
  - The shift-work type may respond to **light therapy.**
  - Oral melatonin may be useful if given 5½ hours before the desired bedtime.

SOMATIC SYMPTOM AND RELATED DISORDERS

Somatic Symptom Disorder

Patients often present with excessive thoughts, anxiety, and behaviors driven by presence of somatic symptoms that is distressing and negatively affects daily life. This may occur with or without any medical illness present. High health care utilization is often present.

Treatment

- Regularly scheduled appointments with one clinician as 1° caregiver.
- Avoid unnecessary diagnostics.
- Psychotherapy.

Conversion Disorder

Characterized by symptoms or deficits of voluntary motor or sensory function (eg, blindness, seizurelike movements, paralysis) incompatible with medical processes. Close temporal relationship to stress or intense emotion.

Diagnosis

- Symptoms unexplained by other medical or neurologic causes.
- Physical exam signs suggesting nonorganic cause of symptoms:
  - Presence of Hoover sign (extension of affected leg when asked to raise the unaffected contralateral leg) when attempting to rule out leg paralysis.
  - Eyes closed and resistant to opening during seizure, negative simultaneous EEG.
  - Tremor disappears with distraction.

Treatment

Psychotherapy.

FACTITIOUS DISORDERS AND MALINGERING

Characterized by the fabrication of symptoms or self-injury to assume the sick role (1° gain). Referred to as "factitious disorder imposed on another" (formerly Munchausen by proxy) when a "caregiver" makes someone else ill and enjoys taking on the role of concerned caregiver.

In **malingering,** patients i**ntentionally cause** or feign symptoms for **2° gain** of **financial benefit** or **housing.**

KEY FACT

Factitious disorders and malingering are distinct from somatoform disorders in that they involve conscious and intentional processes.

KEY FACT

In malingering, patients intentionally simulate illness for personal gain.

Q

A 57-year-old morbidly obese man presents to his physician with concerns about ↑ daytime sleepiness and ↓ work productivity. He recently received multiple divorce threats from his wife for excessive snoring that sounds like "the snort of a steam engine." What long-term complications are of concern for this patient?

Treatment

- Psychotherapy.
- Minimal diagnostics and treatment to avoid reinforcement of behaviors.

KEY FACT

Sexual abusers are usually male and are often known to the victim (and are often family members).

SEXUAL AND PHYSICAL ABUSE

- Most frequently affects women < 35 years of age who:
  - Are experiencing marital discord and are substance abusers or have a partner who is a substance abuser; or
  - Are pregnant, have low socioeconomic status, or have obtained a restraining order.
- Victims of childhood abuse are more likely to become adult victims of abuse.
- **Hx/PE:**
  - Patients typically have **multiple somatic complaints, frequent ER visits,** and **unexplained injuries** with **delayed medical treatment.** They may also **avoid eye contact** or act afraid or hostile.
  - Children may exhibit precocious sexual behavior, **genital or anal trauma, STDs,** UTIs, and psychiatric problems.
  - Other clues include a partner who answers questions for the patient or refuses to leave the examination room.
- **Tx:** Perform a screening assessment of the patient's safety domestically and in her/his close personal relationships. Provide **medical care,** emotional **support, and counseling;** educate the patient about **support services,** and refer appropriately. **Documentation** is crucial.

MNEMONIC

Risk factors for suicide—
SAD PERSONS

Sex (male)
Age (older)
Depression
Previous attempt
Ethanol/substance abuse
Rational thought
Sickness (chronic illness)
Organized plan/access to weapons
No spouse
Social support lacking

KEY FACT

Suicide is the third leading cause of death (after homicide and accidents) among 15- to 24-year-olds in the United States.

SUICIDALITY

- Accounts for 30,000 deaths per year in the United States; the eighth overall cause of death in the United States. One suicide occurs every 17–20 minutes.
- Risk factors include male gender, **age > 45 years,** psychiatric disorders (major depression, presence of psychotic symptoms), a history of an admission to a psychiatric institution, a **previous suicide attempt,** a history of violent behavior, ethanol or substance abuse, recent severe stressors, and a family suicide history (see the mnemonic **SAD PERSONS**).
- Women are more likely to attempt suicide, whereas men are more likely to succeed by virtue of their ↑ use of more lethal methods.
- **Dx:**
  - Perform a comprehensive psychiatric evaluation.
  - Ask about family history, previous attempts, ambivalence toward death, and hopelessness.
  - Ask **directly** about suicidal ideation, intent, and plan, and look for available means.
- **Tx:** A patient who endorses suicidality requires emergent inpatient hospitalization even against his/her will. Suicide risk may ↑ after antidepressant therapy is initiated because a patient's energy to act on suicidal thoughts can return before the depressed mood lifts.

KEY FACT

Emergent inpatient hospitalization is required for patients with suicidal intentions.

A

This patient has obstructive sleep apnea. Serious consequences include leg swelling, hypertension, cor pulmonale, stroke, and clinical depression.

HIGH-YIELD FACTS IN

PULMONARY

Obstructive Lung Disease 448
- Asthma 448
- Bronchiectasis 450
- Chronic Obstructive Pulmonary disease 451

Restrictive Lung Disease 452
- Interstitial Lung disease 452
- Systemic Sarcoidosis 454
- Hypersensitivity Pneumonitis 454
- Pneumoconiosis 454
- Eosinophilic Pulmonary Syndromes 455

Acute Respiratory Failure 456
- Hypoxemia 456
- Acute Respiratory distress Syndrome 456

Pulmonary Vascular Disease 458
- Pulmonary Hypertension/cor Pulmonale 458
- Pulmonary Thromboembolism 459

Neoplasms of the Lungs 461
- Lung Nodules 461
- Lung cancer 461

Pleural Disease 464
- Pleural Effusion 464
- Pneumothorax 465

MNEMONIC

Etiologies of obstructive pulmonary disease—

ABCO

Asthma
Bronchiectasis
Cystic fib osis/COPD
Obstruction (tracheal or bronchial)

KEY FACT

FEV_1/FVC ratio < 70% suggestive of obstructive ventilatory defect and FEV_1/FVC ratio ≥ 70% suggestive of restrictive ventilatory defect.

KEY FACT

Beware—all that wheezes is not asthma! Other conditions that can cause wheezes are foreign body inhalation and COPD (ie, anything causing airway constriction).

KEY FACT

Asthma should be suspected in children with multiple episodes of croup and URIs associated with dyspnea. Childhood eczema is also associated with asthma.

KEY FACT

Asthma triggers include allergens, URIs, cold air, exercise, drugs, and stress.

Obstructive Lung Disease

Characterized by airway narrowing, obstructive lung diseases restrict air movement and often cause air trapping. Figure 2.15-1 illustrates the role of lung volume measurements in the diagnosis of lung disease; Table 2.15-1 and Figures 2.15-1 and 2.15-2 contrast obstructive with restrictive lung diseases.

ASTHMA

Reversible airway obstruction 2° to bronchial hyperreactivity, airway inflammation, mucous plugging, and smooth muscle hypertrophy.

History/Pe

- Usually presents with dry **cough, episodic wheezing,** dyspnea, and/or chest tightness, often worsening at night or in early morning. Aspirin and NSAIDs can also induce asthma. (Samter's triad is asthma, aspirin sensitivity, and nasal polyps.)
- **Examination: Wheezing, prolonged expiration** (↓ I/E ratio), increased **accessory muscle use,** tachypnea, tachycardia, hyperresonance, and possible pulsus paradoxus.
- **Late signs:** ↓ breath sounds (ie, no wheezing), cyanosis, and ↓ O_2 saturation.

Diagnosis

- **Spirometry/PFTs (initial diagnosis):** Essential to diagnose, obstructive pattern (↓ **FEV_1/FVC**); ↑ RV and total lung capacity (TLC). PFTs are often normal between exacerbations.
- **Methacholine challenge:** Tests for bronchial hyperresponsiveness; useful when PFTs are normal but asthma is still suspected.
- **ABGs: Initially with acute respiratory alkalosis and potentially mild hypoxia.** Normalizing P_{CO_2}, respiratory acidosis, and more severe hypoxia may indicate fatigue and impending respiratory failure, **consider if patients are in severe respiratory distress requiring hospitalization.**
- **CXR:** Normal appearance to hyperinflation with flattening of the diaphragm.

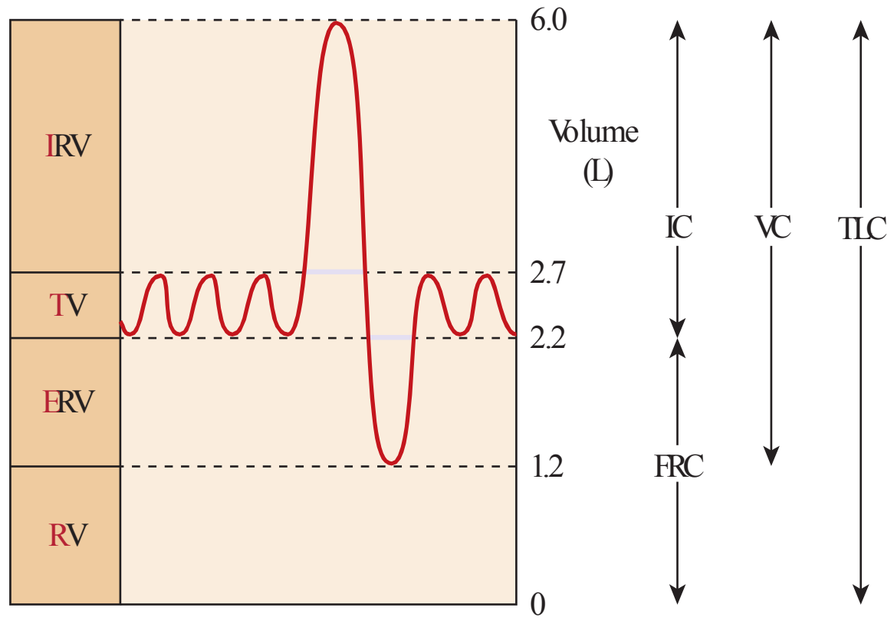


FIGURE 2.15-1. Lung volumes in the interpretation of PFTs. (Reproduced with permission from Le T et al. First Aid for the USMLE Step 1 2015. New York, NY: McGraw-Hill; 2015.)

TABLE 2.15-1. Obstructive vs Restrictive Lung Disease

Test	Normal	Mild	Moderate	Severe
Obstructive				
FEV_1 (% of FVC)	> 75	60–75	40–60	< 40
RV (% of predicted)	80–120	120–150	150–175	> 200
Restrictive				
FVC (% of predicted)	> 80	60–80	50–60	< 50
FEV_1 (% of FVC)	> 75	> 75	> 75	> 75
RV (% of predicted)	80–120	80–120	70–80	70

Treatment

In general, avoid allergens or any potential triggers. See also Tables 2.15-2 and 2.15-3 for management.

- **Acute:**
  - O_2, **bronchodilating agents** (short-acting inhaled β_2-agonists are first-line therapy); **ipratropium** (never used alone for asthma), **systemic corticosteroids,** magnesium (for severe exacerbations).
  - Consider intubation in severe cases or acutely in patients with a P_{CO_2} > 50 mm Hg or a P_{O_2} < 50 mm Hg.

KEY FACT

Corticosteroids inhaled in a **rush** can lead to **thrush**!

KEY FACT

Summary of asthma medications:

- PRN medications—short-acting bronchodilators (eg, albuterol).
- Long-term medications—inhaled corticosteroids, long-acting β_2-agonists (eg, salmeterol), and PO corticosteroids.

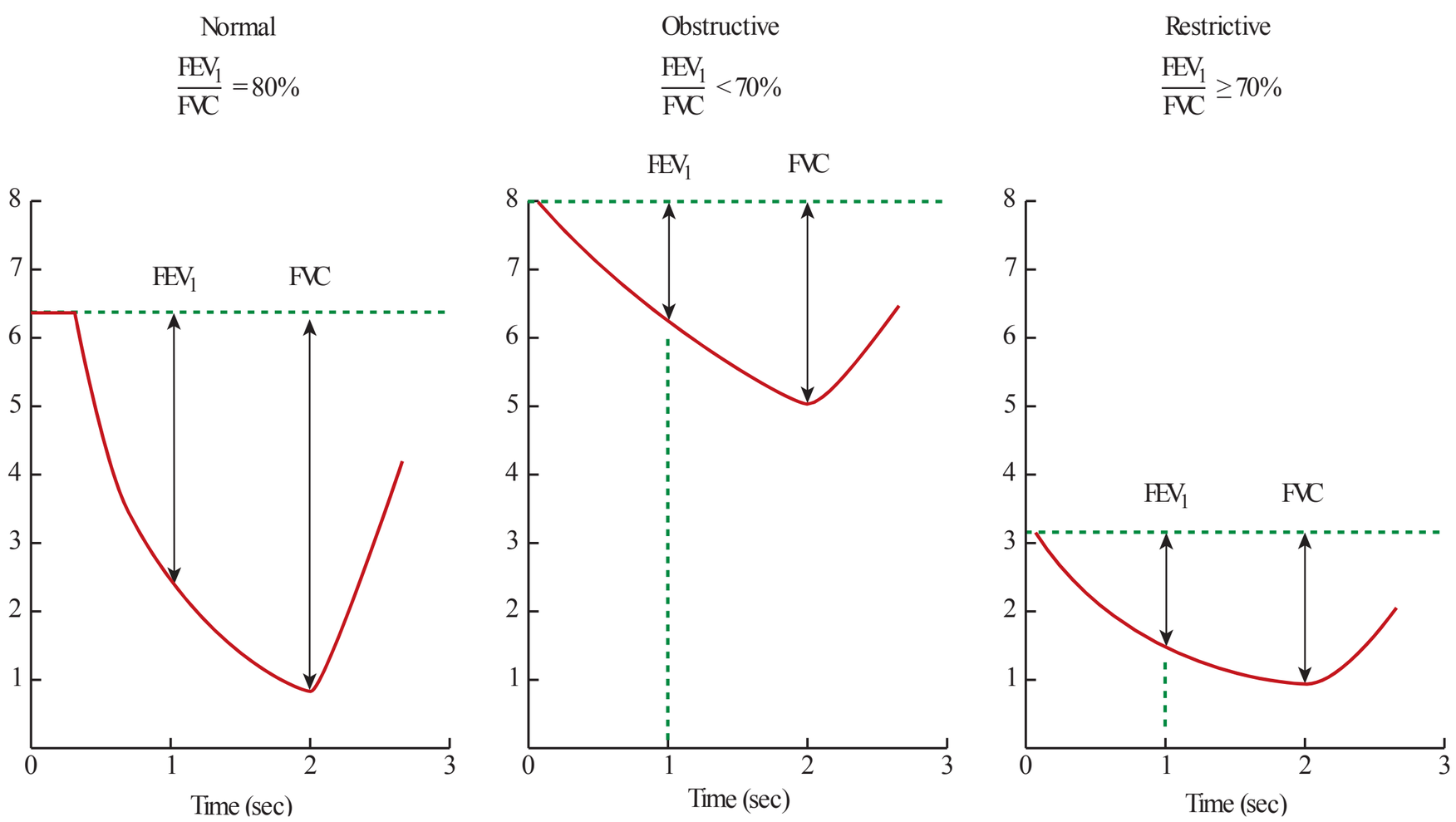


FIGURE 2.15-2. Obstructive vs restrictive lung disease. Shown are typical alterations in lung volumes and capacities in restrictive and obstructive diseases. (Reproduced with permission from Le T et al. First Aid for the USMLE Step 1 2015. New York, NY: McGraw-Hill; 2015.)

TABLE 2.15-2. Common Asthma Medications and Their Mechanisms

Drug	Mechanism of Action
β_2-agonists	**Albuterol:** Short acting. Relaxes bronchial smooth muscle (β_2-adrenoceptors). **Salmeterol:** Long-acting agent for prophylaxis.
Corticosteroids	**Inhaled corticosteroids** are first-line treatment for long-term control of asthma. **Beclomethasone, prednisone:** Inhibit the synthesis of cytokines.
Muscarinic antagonists	**Ipratropium:** Competitively blocks muscarinic receptors, preventing bronchoconstriction.
Methylxanthines	**Theophylline:** Probably causes bronchodilation by inhibiting phosphodiesterase, thereby decreasing cAMP hydrolysis and increasing cAMP levels. Usage is limited because of its narrow therapeutic-toxic index (cardiotoxicity, neurotoxicity).
Cromolyn	Prevents the release of vasoactive mediators from mast cells. Useful for exercise-induced bronchospasm. **Effective only for the prophylaxis** of asthma; not effective during an acute attack. Toxicity is rare.
Antileukotrienes	**Zileuton:** A 5-lipoxygenase pathway inhibitor. Blocks conversion of arachidonic acid to leukotrienes. **Montelukast, zafirlukast:** Block leukotriene receptors.

MNEMONIC

Meds for asthma exacerbations—

ASTHMA

Albuterol
Steroids
Theophylline (rare)
Humidified $_2$
Magnesium (severe exacerbations)
Anticholinergics

- **Chronic:**
  - Administer long-acting inhaled **bronchodilators** and/or inhaled corticosteroids, systemic **corticosteroids,** cromolyn, or, rarely, theophylline.
  - Montelukast and other leukotriene antagonists are oral adjuncts to inhalant therapy.

BRONCHIECTASIS

A disease caused by recurrent infection and inflammation in the bronchi/bronchioles that lead to fibrosis, remodeling, and **permanent dilation of bronchi** (see Figure 2.15-3).

TABLE 2.15-3. Medications for the Chronic Treatment of Asthma

Type	Symptoms (Day/Night)	FEV_1	Medications
Mild intermittent	≤ 2 days/week ≤ 2 nights/month	≥ 80%	No daily medications. PRN short-acting bronchodilator.
Mild persistent	> 2 times/week but < 1 time/day > 2 nights/month	≥ 80%	Daily low-dose inhaled corticosteroids. PRN short-acting bronchodilator.
Moderate persistent	Daily > 1 night/week	60–80%	Low- to medium-dose inhaled corticosteroids + long-acting inhaled β_2-agonists. PRN short-acting bronchodilator.
Severe persistent	Continual, frequent	≤ 60%	High-dose inhaled corticosteroids + long-acting inhaled β_2-agonists. Possible PO corticosteroids. PRN short-acting bronchodilator.

History/Pe

- Presents with chronic productive cough accompanied by frequent bouts of yellow or green sputum production, dyspnea, and possible hemoptysis and halitosis.
- Associated with a history of cystic fibrosis (CF), pulmonary infections, hypersensitivity, immunodeficiency, localized airway obstruction, aspiration, autoimmune disease, or IBD, but seen more closely in allergic bronchopulmonary aspergillosis, tuberculosis, and non-tuberculous mycobacterium such as Mycobacterium avium complex (MAC).
- Examination reveals rales, wheezes, rhonchi, purulent mucus, and occasional hemoptysis.

Diagnosis

- **CXR:** Shows ↑ bronchovascular markings and **tram lines** (parallel lines outlining dilated bronchi as a result of peribronchial inflammation and fibrosis).
- **High-resolution CT (definitive test): Dilated airways** (ie, larger than pulmonary arteries) and ballooned cysts are seen at the end of the bronchus (mostly lower lobes).
- Spirometry shows a ↓ FEV_1/FVC ratio consistent with obstruction.

Treatment

- **Medications:** Antibiotics (oral and inhaled, for bacterial infections), consider inhaled corticosteroids.
- **Lifestyle:** Bronchopulmonary hygiene (cough control, postural drainage, chest physiotherapy).
- **Surgery:** Consider lobectomy for localized disease or lung transplantation for severe disease.

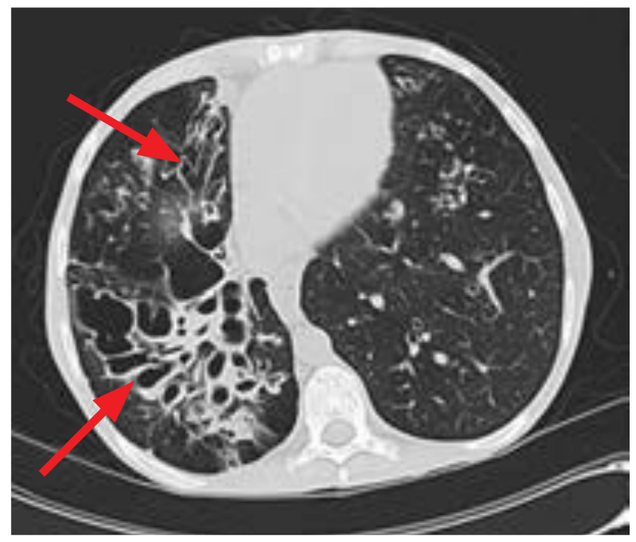


FIGURE 2.15-3. Bronchiectasis. Chest CT demonstrates markedly dilated and thick-walled airways (arrows) consistent with bronchiectasis in this CF patient. (Reproduced with permission from USMLE-Rx.com.)

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

A disease with ↓ lung function associated with airflow obstruction. Generally 2° to chronic bronchitis and/or emphysema, which are distinguished as follows:

- **Chronic bronchitis:** Productive cough for > 3 months per year for 2 consecutive years (clinical diagnosis).
- **Emphysema:** Destruction and dilation of structures distal to the terminal bronchioles (pathologic diagnosis) that may be 2° to **smoking (centrilobular)** or to **α_1-antitrypsin deficiency (panlobular).**

History/Pe

- Symptoms are minimal or nonspecific until the disease is advanced.
- The clinical spectrum is shown in Table 2.15-4 (most patients are a combination of the two phenotypes).
- Look for the classic barrel chest, use of accessory chest muscles, JVD, end-expiratory wheezing, dyspnea on exertion, and muffled breath sounds.

KEY FACT

In COPD patients with chronic hypercapnia, high concentrations of O_2 may worsen ventilatory to perfusion mismatch and worsen the acute respiratory acidosis.

KEY FACT

Supplemental O_2 and smoking cessation are the only interventions proven to improve survival in patients with COPD.

KEY FACT

Treatments for acute asthma and COPD exacerbations both involve β_2-agonists and corticosteroids. During an acute COPD exacerbation, antibiotics may also be given. During an acute asthma exacerbation, magnesium can be given.

TABLE 2.15-4. COPD Subtypes

COPD Type	Nickname	Definition	Appearance	Acid-base status
Emphysema	"Pink puffer"	Productive cough > 3 months × 2 years.	Thin, wasted appearance with pursed lips, minimal cough.	Late hypercarbia/hypoxia (hence pink).
Chronic bronchitis	"Blue bloater"	Terminal airway destruction and dilation.	Overweight, edematous.	Early hypercarbia/hypoxia (hence blue).

MNEMONIC

Treatment for COPD—

COPD

Corticosteroids
Oxygen
Prevention (**cigarette-smoking cessation,** pneumococcal and influenza vaccines)
Dilators (β_2-agonists, anticholinergics)

Diagnosis

- **PFTs (definitive diagnosis): ↓ FEV_1/FVC,** normal or ↓ FVC; reduced FEV_1, normal or ↑ TLC (emphysema, asthma); ↓ diffusing capacity of the lung for carbon monoxide (DL_{CO}) (in emphysema).
- **CXR: Hyperinflated lungs,** ↓ lung markings with flat diaphragms, and a thin-appearing heart and mediastinum are sometimes seen. Parenchymal **bullae** or subpleural **blebs** (pathognomonic of emphysema) are also seen (see Figure 2.15-4).
- **ABGs:** Hypoxemia with acute or chronic respiratory acidosis (↑ P_{CO_2}).
- **Gram stain and sputum culture:** Consider if bacterial infection is suspected (eg, fever, productive cough, new infiltrate on CXR).

Treatment

See Table 2.15-5.

MNEMONIC

If the lungs AIN'T compliant:

Alveolar (edema, hemorrhage, pus)
Interstitial lung disease (idiopathic interstitial pneumonias), **I**nflammatory (sarcoid, cryptogenic organizing pneumonia), **I**diopathic pulmonary fibrosis (IPF)
Neuromuscular (myasthenia, phrenic nerve palsy, myopathy)
Thoracic wall (kyphoscoliosis, obesity, ascites, pregnancy, ankylosing spondylitis)

Restrictive Lung Disease

Characterized by a loss of lung compliance, restrictive lung diseases result in ↑ lung stiffness and ↓ lung expansion. Table 2.15-1 and Figure 2.15-2 contrast obstructive with restrictive lung disease. The etiologies of restrictive lung disease are shown in the mnemonic **AIN'T.**

INTERSTITIAL LUNG DISEASE

A heterogeneous group of disorders characterized by **inflammation** and/or **fibrosis** of the interstitium.

- Advanced disease: Cystic spaces develop in the lung periphery ("honeycombing").



A B

FIGURE 2.15-4. COPD. PA **(A)** and lateral **(B)** radiographs of a patient with emphysema show hyperinflation with large lung volumes, flattening of the diaphragm, and minimal peripheral vascular markings. (Reproduced with permission from USMLE-Rx.com.)

TABLE 2.15-5. COPD Treatment

	Medications	Oxygen	Lifestyle
Acute exacerbation	**Inhaled β_2-agonists** (albuterol) and **anticholinergics** (ipratropium, tiotropium), IV ± inhaled **corticosteroids, antibiotics.**	**Supplemental O_2** Severe cases: noninvasive ventilation with bilevel **positive airway pressure (BiPAP)** or **intubation** (if severe hypoxemia/ hypercapnia, respiratory fatigue, changes in mental status).	N/A.
Chronic COPD	Inhaled β_2-**agonists, anticholinergics** (tiotropium), systemic or inhaled **corticosteroids.**	Give **supplemental O_2** if patient has (1) hypoxemia (2) right heart failure, or (3) polycythemia.	Smoking cessation, pneumococcal and flu accines.

- Subgroups: (1) **Exposure related** (eg, "coal worker's pneumoconiosis," asbestosis, silicosis, berylliosis, hypersensitivity pneumonitis, radiation-induced injury); (2) **ILD associated with systemic disease or connective tissue diseases** (polymyositis/dermatomyositis, sarcoidosis, amyloidosis, vasculitis, dermatomyositis, CREST syndrome); (3) **idiopathic** (idiopathic pulmonary fibrosis, cryptogenic organizing pneumonia, acute interstitial pneumonia).

History/Pe

- Presents with **shallow, rapid breathing;** dyspnea with exertion; and a chronic nonproductive cough.
- Patients may have cyanosis, inspiratory squeaks, fine or "Velcro-like" crackles, clubbing, or right heart failure.

Diagnosis

- **CXR/CT (initial test):** Reticular, nodular, or ground-glass pattern; **"honeycomb"** pattern (severe disease).
- **PFTs: ↓ TLC, ↓ FVC, ↓ DL_{CO} (initial test):** May be normal if the cause is extrapulmonary, **normal FEV_1/FVC.** Serum markers of connective tissue diseases should be obtained if clinically indicated.
- **Surgical biopsy (definitive test):** Often to confirm a diagnosis of IPF (see Figure 2.15-5).

Treatment

- **Supportive:** Avoid exposure to causative agents.
- **Medications:** Anti-inflammatory/immunosuppressive agents for some disease (eg, **corticosteroids**), antifibrotic agents (pirfenidone, nintedanib) for IPF.
- **Surgery:** Lung transplantation may be indicated at late stages of IPF.

KEY FACT

Medications and interventions that can cause or contribute to interstitial lung disease include **amiodarone,** busulfan, nitrofurantoin, bleomycin, radiation, and long-term high O_2 concentration (eg, PaO_2 ventilators).

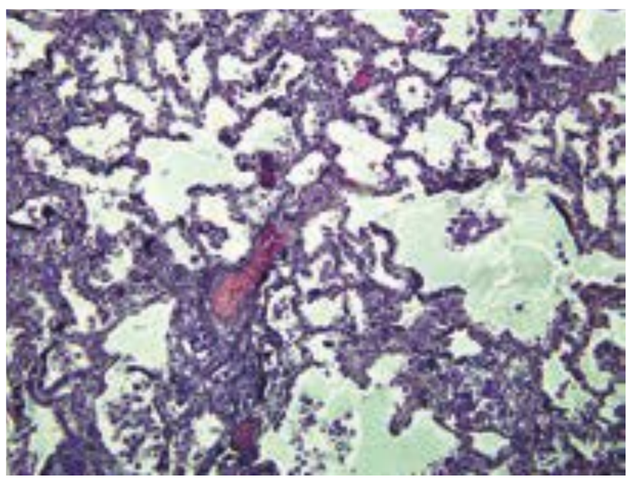


FIGURE 2.15-5. Idiopathic pulmonary fibrosis Lung biopsy specimen demonstrating increased interstitial fibrosis and nonspecific inflammation with alveolar thickening. (Reproduced with permission from USMLE-Rx.com.)

Q

A 10-year-old child with a history of asthma on daily fluticasone has been using an albuterol inhaler once a day for several weeks. What changes should be made to the current regimen?

SYSTEMIC SARCOIDOSIS

A multisystem disease of unknown etiology characterized by **noncaseating granulomas.** Most commonly found in **black women** and Northern European whites; most often arises in the third or fourth decade of life.

History/Pe

- **Hx:** Can present with **fever, cough, malaise,** weight loss, dyspnea, and **arthritis.**
- **Examination:** Lungs, liver, eyes, skin (erythema nodosum, violaceous skin plaques), nervous system, heart, and kidney may be affected.

Diagnosis

- **CXR/CT (initial test):** Radiographic findings of **lymphadenopathy** and **nodules** are used to stage the disease.
- **Biopsy (definitive test):** Lymph node biopsy or transbronchial/video-assisted thoracoscopic lung biopsy reveals **noncaseating granulomas.**
- **PFTs:** Restrictive or obstructive pattern and ↓ diffusion capacity.
- **Other findings:** ↑ **serum ACE levels** (neither sensitive nor specific), **hypercalcemia,** hypercalciuria, ↑ alkaline phosphatase (with liver involvement), lymphopenia, cranial nerve defects, arrhythmias.

Treatment

Systemic **corticosteroids** are indicated for deteriorating respiratory function, constitutional symptoms, hypercalcemia, or extrathoracic organ involvement.

HYPERSENSITIVITY PNEUMONITIS

Alveolar thickening and noncaseating granulomas 2° to environmental exposure (eg, mold, hot tubs, cockatiels, down feather antigens).

History/Pe

- **Acute:** Dyspnea, fever, malaise, shivering, and cough starting 4–6 hours after exposure. Gather a job/travel history to determine exposure.
- **Chronic:** Patients present with progressive dyspnea; examination reveals fine bilateral rales.

Diagnosis

The appearance on CXR/CT is variable, but upper lobe fibrosis is a common feature of chronic disease.

Treatment

Avoid ongoing exposure to inciting agents; give corticosteroids to ↓ chronic inflammation.

PNEUMOCONIOSIS

Risk factors include prolonged occupational exposure and inhalation of small inorganic dust particles.

History/Pe/Diagnosis

Table 2.15-6 outlines the findings and diagnostic criteria associated with common pneumoconioses.

MNEMONIC

Learning the features of sarcoid can be—

GRUELING

Granulomas
a**R**thritis
Uveitis
Erythema nodosum
Lymphadenopathy (particularly hilar, seen on CXR)
Interstitial fibrosis
Negative TB test
Gammaglobulinemia

KEY FACT

Löfgren syndrome is a type of sarcoidosis with the following triad: arthritis, erythema nodosum, and bilateral hilar adenopathy.

A

This child has moderate persistent asthma with daily symptoms. The patient will benefit from an inhaled corticosteroid and a long activating β_2-agonist, such as salmeterol, for prevention of symptoms.

TABLE 2.15-6. Diagnosis of Pneumoconioses

Disorder	History	Imaging findings[a]	Complications
Asbestosis	Work involving the manufacture of tile or brake linings, insulation, construction, demolition, or shipbuilding. Presents 15–20 years after initial exposure.	**Linear opacities** at lung bases and interstitial fibrosis; calcified pleural plaques are indicative of benign pleural disease (see Figure 2.15-6).	↑ risk of mesothelioma (rare) and lung cancer; the risk of lung cancer is higher in smokers.
Coal worker's disease	Work in underground coal mines.	Small nodular opacities (< 1 cm) in upper lung zones.	**Progressive massive fibrosis.**
Silicosis	Work in mines or quarries or with glass, pottery, or silica.	Small (< 1-cm) nodular opacities in upper lung zones; **eggshell calcifications.**	↑ **risk of TB;** need annual TB skin test. Progressive massive fibrosis.
Berylliosis	Work in high-technology fields such as **aerospace, nuclear, and electronics plants;** ceramics industries; foundries; plating facilities; dental material sites; and dye manufacturing.	Diffuse infiltrates; hilar adenopathy.	**Requires chronic corticosteroid treatment.**

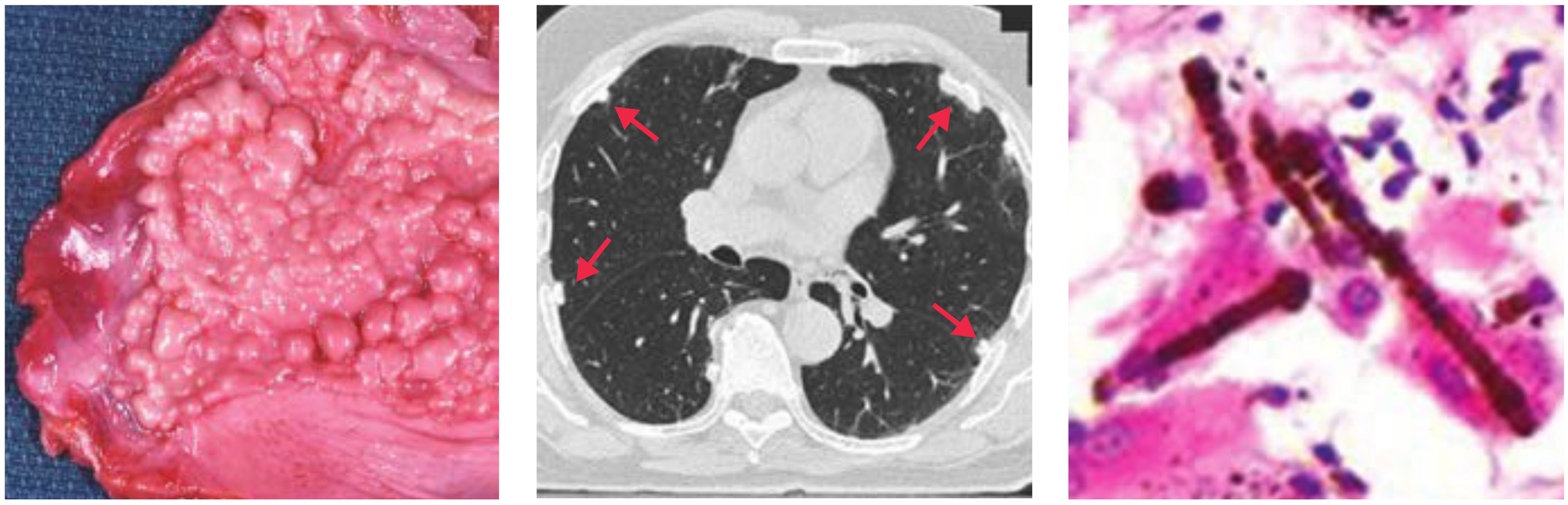
[a]Spirometry: consistent with restrictive disease.

Treatment

Avoid triggers; supportive therapy and supplemental O_2.

EOSINOPHILIC PULMONARY SYNDROMES

A diverse group of disorders characterized by eosinophilic pulmonary infiltrates and abnormal peripheral blood eosinophilia. Includes allergic broncho-



A B C

FIGURE 2.15-6. Asbestosis. (A) Pleural plaques on gross pathology. **(B)** Pleural plaques on CT. **(C)** Ferruginous bodies in alveolar septum. (Part A used with permission of Dr. Yale Rosen. Part B reproduced with permission of Miles SE, Sandrini A, Johnson AR, et al. Clinical consequences of asbestos-related diffuse pleural thickening: a review, J Occup Med Toxicol 2008 Sep 8;3:20. Part C reproduced with permission of Nephron.)

pulmonary aspergillosis, Löffler syndrome, acute eosinophilic pneumonia, and drug-induced (eg, NSAIDs, nitrofurantoin, sulfonamides).

History/Pe

Presents with dyspnea, cough, potentially blood-tinged sputum, and/or fever.

Diagnosis

- **CBC:** May reveal peripheral eosinophilia.
- **CXR:** Shows pulmonary infiltrates.

Treatment

Removal of the extrinsic cause or treatment of underlying infection (eg, helminths) if identified. Corticosteroid treatment may be used.

Acute Respiratory Failure

HYPOXEMIA

↓ P_{O_2}; causes include **ventilation-perfusion (V/Q) mismatch,** right-to-left **shunt, hypoventilation,** low inspired O_2 content (important at altitudes), and **diffusion impairment.**

History/Pe

Findings depend on the etiology. ↓ **SpO_2 saturation,** cyanosis, tachypnea, shortness of breath, pleuritic chest pain (caused by wheezing, coughing), and altered mental status may be seen.

KEY FACT

If the problem is hypoventilation or low inspired oxygen, the A-a gradient will be normal. If the problem is V/Q mismatch or shunting, the A-a gradient will increase.

Diagnosis

- **ABGs (initial test):** Calculate the **alveolar-arterial (A-a) oxygen gradient:** $([P_{atm} - 47] \times Fi_{O_2} - [Pa_{CO_2}/0.8]) - Pa_{O_2}$.
- **Pulse oximetry:** Demonstrates ↓ **SpO_2** saturation.
- **CXR:** To evaluate for an infiltrative process (eg, pneumonia), atelectasis, a large pleural effusion, or pneumothorax and to assess for ARDS. An ↑ A-a gradient suggests shunt, **V/Q mismatch,** or **diffusion impairment.** Figure 2.15-7 summarizes the approach toward hypoxemic patients.

TABLE 2.15-7. Mechanical Ventilator Parameters Affecting Oxygenation and Ventilation

↑ Oxygenation	↑ Ventilation
↑ Fi_{O_2}	↑ respiratory rate
↑ PEEP	↑ tidal volume

Treatment

- Address the underlying etiology.
- Administer O_2 before initiating evaluation.
- ↑ oxygenation parameters if the patient is on mechanical ventilation (see Table 2.15-7).
- In **hypercapnic patients,** ↑ ventilation to ↑ CO_2 exchange.

ACUTE RESPIRATORY DISTRESS SYNDROME

- Respiratory failure with refractory **hypoxemia, ↓ lung compliance,** and noncardiogenic **pulmonary edema** with a Pa_{CO_2}/Fi_{O_2} ratio ≤ 300.
- Pathogenesis is thought to be dependent on endothelial injury. Common triggers include **sepsis,** pneumonia, aspiration, multiple blood transfusions, inhaled/ingested toxins, and trauma. Overall mortality is 30–40%.

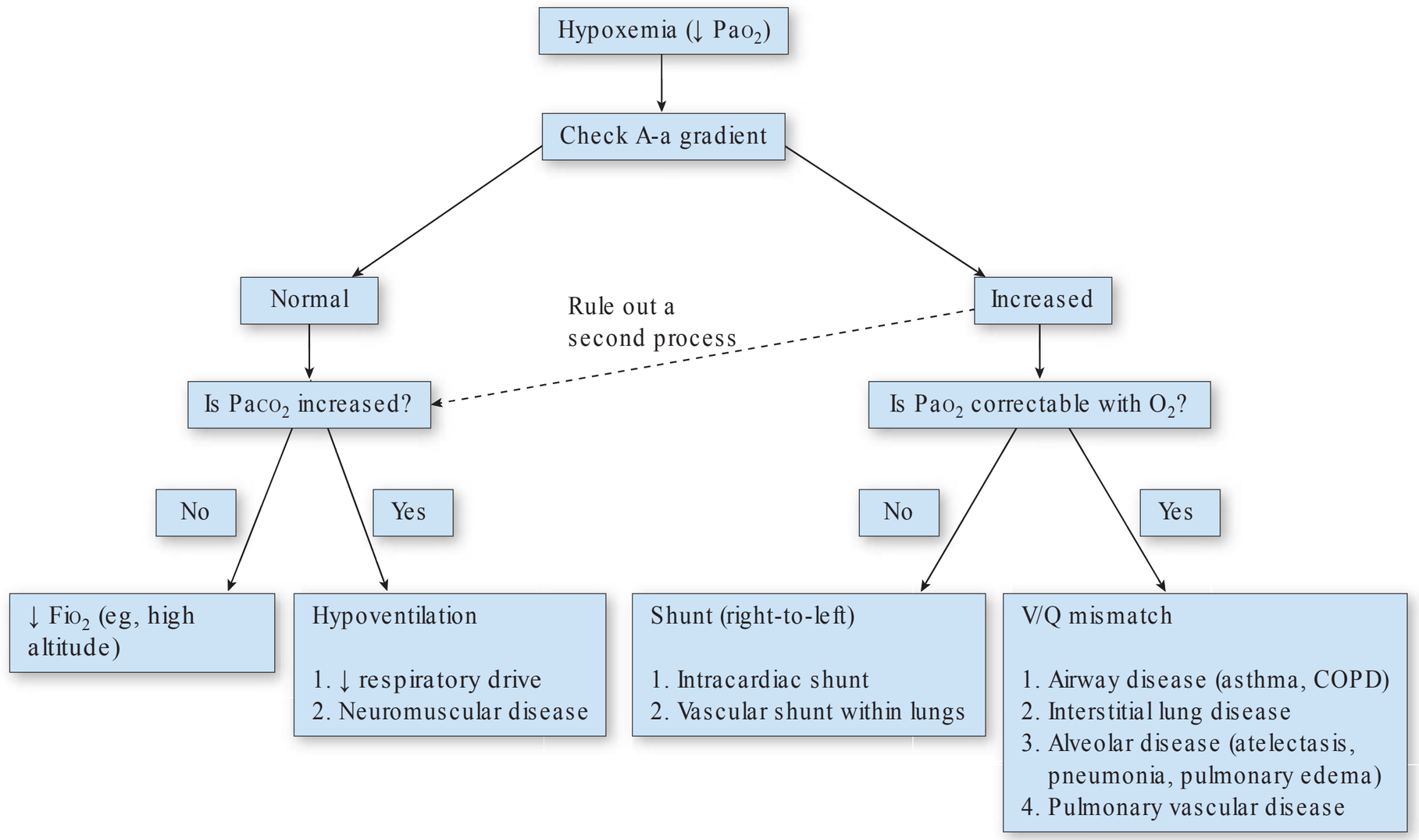


FIGURE 2.15-7. Determination of the mechanism of hypoxia.

History/Pe

Presents with **acute-onset** (12–48 hours) tachypnea, dyspnea, and tachycardia ± fever, cyanosis, labored breathing, diffuse high-pitched rales, and hypoxemia in the setting of one of the systemic inflammatory causes or exposure. Additional findings are as follows:

- **Phase 1 (acute injury):** Normal physical examination; possible respiratory alkalosis.
- **Phase 2 (6–48 hours):** Hyperventilation, hypocapnia, widening A-a gradient.
- **Phase 3:** Acute respiratory failure, tachypnea, dyspnea, ↓ lung compliance, scattered rales, diffuse chest opacity on CXR (see Figure 2.15-8).
- **Phase 4:** Severe hypoxemia unresponsive to therapy; ↑ intrapulmonary shunting; metabolic and respiratory acidosis.



FIGURE 2.15-8. AP CXR showing a diffuse alveolar filling pattern ° to ARDS. (Reproduced with permission from Kasper DL et al. Harrison's Principles of Internal Medicine, 16th ed. New York, NY: McGraw-Hill; 2005.)

Diagnosis

The criteria for ARDS diagnosis (according to the Berlin definition) are as follows:

- Acute onset (< 1 week) of respiratory distress.
- A Pao_2/Fio_2 ratio ≤ 300 with PEEP/CPAP ≥ 5 cm H_2O.
- Bilateral pulmonary infiltrates on CXR.
- Respiratory failure not completely explained by heart failure.

Treatment

- Treat the underlying disease and maintain adequate perfusion to prevent end-organ damage.
- Mechanical ventilation with low tidal volumes (4–6 cc/kg of ideal body weight) to minimize ventilator-induced lung injury.
- Use PEEP to recruit collapsed alveoli, and titrate PEEP and Fio_2 to achieve adequate oxygenation.
- Goal oxygenation is Pao_2 > 55 mm Hg or **Sao_2 > 88%**
- Slowly wean patients from ventilation, and follow with extubation trials (see Table 2.15-8).

Pulmonary Vascular Disease

PULMONARY HYPERTENSION/COR PULMONALE

Cor pulmonale is right-sided heart failure due to pulmonary hypertension.

A mean pulmonary arterial pressure of > 25 mm Hg (normal = 15 mm Hg). Five classification categories were defined in 2008 with revisions in 2013:

- Pulmonary arterial hypertension.
- ↑ pulmonary venous pressure from left-sided **heart disease.**

TABLE 2.15-8. Criteria for Extubation from Mechanical Ventilation[a]

Parameter	Value
Pulmonary mechanics	
Frequency/TV ratio (most predictive of successful extubation)	< 105
Vital capacity	> 10–15 mL/kg
Resting minute ventilation (TV × rate)	> 10 L/min
Spontaneous respiratory rate	< 33 breaths/min
Lung compliance	> 100 mL/cm water
Negative inspiratory force	< –25 cm water
Oxygenation	
A-a gradient	< 300–500 mm Hg
Shunt fraction	< 15%
Po_2 (on 40% Fio_2)	> 70 mm Hg
Pco_2	< 45 mm Hg

[a]Patients who meet these criteria are typically given a weaning trial with minimal ventilator support and light sedation to determine if they are ready for extubation.

- Hypoxic vasoconstriction 2° to chronic lung disease.
- Chronic thromboembolic disease.
- Pulmonary hypertension with an unclear, multifactorial etiology.

History/Pe

- Presents with dyspnea on exertion, fatigue, lethargy, syncope with exertion, chest pain, and symptoms of right-sided CHF (edema, abdominal distention, JVD).
- **History:** COPD, interstitial lung disease, heart disease, sickle cell anemia, emphysema, and pulmonary emboli.
- **Examination:** Loud, palpable S2 (often split), a flow murmur, an S4, or a parasternal heave. Patient may also be hypoxemic, especially on exertion.

Diagnosis

- CXR shows enlargement of central pulmonary arteries.
- ECG demonstrates RVH.
- Echocardiogram (initial test) and right heart catheterization (definitive test) may show signs of right ventricular overload and may aid in the diagnosis of the underlying cause.

Treatment

Supplemental O_2, anticoagulation, vasodilators, and diuretics if symptoms of right-sided CHF are present. Treat underlying causes of 2° pulmonary hypertension. Some treatments for pulmonary arterial hypertension include prostanoids, endothelin receptor antagonists, and phosphodiesterase inhibitors. Some patients have vasoreactivity and respond well to high-dose calcium channel blockers.

KEY FACT

Causes of pulmonary hypertension include left heart failure, mitral valve disease, and ↑ resistance in the pulmonary veins, including hypoxic vasoconstriction.

PULMONARY THROMBOEMBOLISM

An occlusion of the pulmonary vasculature by a blood clot. **Ninety-five percent of emboli originate from DVTs** in the deep leg veins. Often leads to pulmonary infarction, right heart failure, and hypoxemia.

History/Pe

- Factors predisposing to thromboembolism are summarized by Virchow triad (see Table 2.15-9).
- Presents with **sudden-onset or subacute dyspnea, pleuritic chest pain, low-grade fever,** cough, tachypnea, tachycardia, and, rarely, hemoptysis.

TABLE 2.15-9. Virchow Triad for Venous Thrombosis

VeNous STasis	eNdoThelial iNjury	hypercoagulabiliTy
Immobility	Trauma	Pregnancy, postpartum
CHF	Surgery	Cigarette use
Obesity	Recent fracture	OCP use
↑ central venous pressure	Previous DVT	Coagulation disorders (eg, protein C/protein S deficiency, factor V Leiden)
		Malignancy
		Severe burns

KEY FACT

Other etiologies of embolic disease include postpartum status (amniotic fluid emboli), fracture (fat emboli), cardiac surgery (air emboli), and endovascular procedure (cholesterol emboli).

Q 1

A 25-year-old man in the ICU is intubated following an acute asthma exacerbation. A repeat ABG is sent after intubation and shows a pH of 7.6, a $Paco_2$ of 33 mm Hg, and an HCO_3^- of 26 mEq/L. What adjustments, if any, would you make to the ventilator settings?

Q 2

A 25-year-old black woman presents with painful bumps on her shins, weight loss, and cough. Examination reveals a prominent 1-cm right axillary lymph node. What is the next best step for diagnosis?

- May have history of immobility (long plane ride, bed-bound, etc.)
- Hypoxia and hypocarbia are seen with resulting respiratory alkalosis.
- Examination may reveal a loud P_2 and prominent jugular A waves with right heart failure.

Diagnosis

- **D-dimer (initial test if low suspicion):** most useful as a "rule-out" test in patients with low clinical suspicion (sensitive, not specific). High negative predictive value.
- **CT pulmonary angiogram with IV contrast**/spiral CT (definitive test): Sensitive and specific for pulmonary embolism (PE); see Figure 2.15-9.
- **ABGs:** Respiratory alkalosis (2° hyperventilation, P_{O_2} < 80 mm Hg).
- **CXR:** May show atelectasis, pleural effusion, **Hampton hump** (a wedge-shaped infarct), Westermark sign (oligemia/collapse of vessels seen distal to PE).
- **ECG:** Most commonly reveals **sinus tachycardia.** The classic triad of **S1Q3T3 is rare**—acute right heart strain with an S wave in lead I, a Q wave in lead III, and an inverted T wave in lead III.
- **V/Q scan:** May reveal areas of mismatch to predict low, indeterminate, or high probability of PE; use if contraindications to CT scan (↑ Cr [contraindication to contrast], pregnancy [contraindication to radiation]). Sensitive for PE, but not specific, especially if there is underlying lung disease.
- **Lower extremity venous ultrasound:** Can detect a clot that may have given off PE, not used to diagnose the PE. Specific and sensitive for DVT; specific but not sensitive for PE.

MNEMONIC

VIRchow triad:

Vascular trauma
Increased coagulability
Reduced blood fl w (stasis)

KEY FACT

Dyspnea, tachycardia, and a normal CXR in a hospitalized and/or bedridden patient should raise suspicion of PE.

Treatment

- **Anticoagulation:**
  - **Acute:** Heparin (bolus then heparin infusion or low-molecular-weight heparin [LMWH] subcutaneously).
  - **Chronic:** Anticoagulation for 3–6 months or during predisposition (goal INR = 2–3).
- **IVC filter:** Indicated in patients with a documented lower extremity DVT if anticoagulation is contraindicated or if patients experience recurrent emboli while anticoagulated.
- **Thrombolysis:** Indicated in cases of massive PE causing right heart failure and hemodynamic instability.

1 **A**

This patient has an uncompensated respiratory alkalosis due to ↑ ventilation. To ↓ ventilation, tidal volume can be ↓ or respiratory rate can be slowed.

2 **A**

This is presumed sarcoidosis. Biopsy of the right axillary lymph node is the next best step for diagnosis and is less invasive than transbronchial lung biopsy.

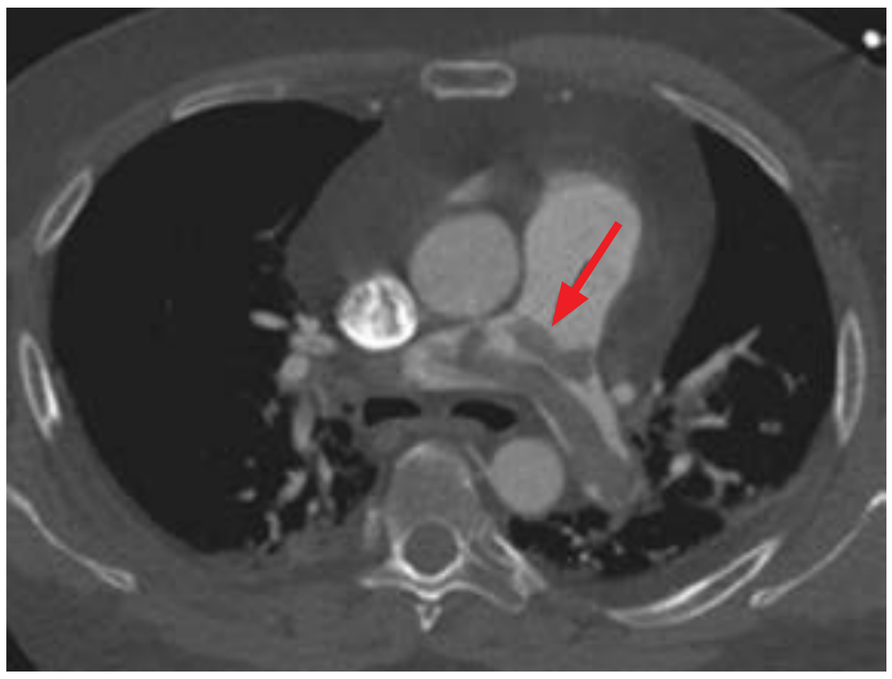


FIGURE 2.15-9. Pulmonary embolus. Axial slice from a CT pulmonary angiogram shows a pulmonary embolus extending from the main pulmonary artery into the right and left pulmonary arteries, consistent with a saddle embolus. (Reproduced with permission from Chen MY et al. Basic Radiology, 2nd ed. New York, NY: McGraw-Hill; 2011.)

- **DVT prophylaxis:** Treat all immobile patients; give **subcutaneous heparin** or LMWH, intermittent compression of the lower extremities (less effective), and **early ambulation (most effective).**

Neoplasms of the Lungs

LUNG NODULES

Commonly found on CXRs. History, physical examination, and imaging features help guide treatment (see Table 2.15-10).

History/Pe

Often asymptomatic, or patients may present with chronic cough, dyspnea, and shortness of breath. Always inquire about smoking and exposure history, which are associated with greater cancer risk.

Treatment

- **Surgical resection** is indicated for nodules at high risk for malignancy. Low-risk nodules can be followed with serial **CXR or CT.**
- An invasive diagnostic procedure is indicated if the size of the nodule ↑.

KEY FACT

Lung nodule clues based on the history:
- Recent immigrant—think TB.
- From the southwestern United States—think coccidioidomycosis.
- From the Ohio River Valley—think histoplasmosis.

LUNG CANCER

The leading cause of **cancer death** in the United States. Risk factors include tobacco smoke (except for bronchoalveolar carcinoma) and radon or asbestos exposure. Types are as follows (see also Table 2.15-11):

- **Small cell lung cancer (SCLC):**
  - Highly correlated with **cigarette exposure.** Central location (see Figure 2.15-10), **neuroendocrine origin;** associated with paraneoplastic syndromes (see Table 2.15-12).
  - Metastases are often found on presentation in intrathoracic and extrathoracic sites such as brain, liver, and bone.
- **Non–small cell lung cancer (NSCLC):** Group of cancers, with the most common types being adenocarcinoma, squamous cell carcinoma (SCC), and large cell carcinoma. These cancers are less likely than SCLC to metastasize at an early stage.

KEY FACT

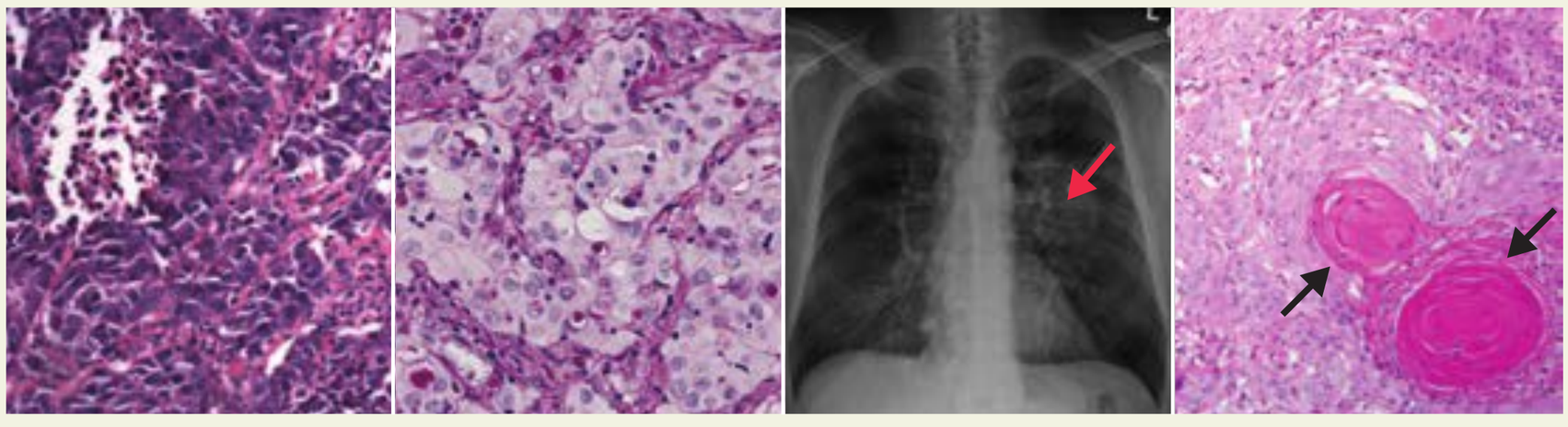
Squamous and **S**mall cell cancers are **S**entral lesions.

TABLE 2.15-10. Characteristics of Benign and Malignant Lung Nodules

Benign	Malignant
Age < 35	Age > 45–50
Nonsmoker	Smoker
No change from old film	New or enlarging lesions
Central, uniform, or popcorn calcification	Absent or irregular calcification
Smooth margins	Irregular margins
Size < 2 cm	Size > 2 cm

TABLE 2.15-11. Small Cell and Non–Small Cell Lung Cancers

Type	Location	Characteristics	Histology
		Small Cell	
Small cell (oat cell) carcinoma	Central	Undifferentiated → very aggressive. May produce ACTH (Cushing syndrome), SIADH, or Antibodies against presynaptic Ca^{2+} channels (Lambert-Eaton myasthenic syndrome) or neurons (paraneoplastic myelitis/encephalitis). Amplification of myc oncogenes common. Inoperable; treat with chemotherapy.	Neoplasm of neuroendocrine Kulchitsky cells → small dark blue cells (see Figure A below). Chromogranin A ⊕.
		Non–Small Cell	
Adenocarcinoma	Peripheral	Most common lung cancer in nonsmokers and overall (except for metastases). Activating mutations include KRAS, EGFR, and ALK. Associated with hypertrophic osteoarthropathy (clubbing). Bronchioloalveolar subtype (adenocarcinoma in situ): CXR often shows hazy infiltrates similar to pneumonia; excellent prognosis.	Glandular pattern on histology, often stains mucin ⊕ (see Figure B below). Bronchioloalveolar subtype: grows along alveolar septa → apparent "thickening" of alveolar walls.
Squamous cell carcinoma	Central	Hilar mass arising from bronchus (see red arrow in Figure C below); Cavitation; Cigarettes; hyperCalcemia (produces PTHrP).v	Keratin pearls (see arrows in Figure D below) and intercellular bridges.
Large cell carcinoma	Peripheral	Highly anaplastic undifferentiated tumor; poor prognosis. Less responsive to chemotherapy; removed surgically.	Pleomorphic giant cells. Can secrete β-hCG.
Bronchial carcinoid tumor	—	Excellent prognosis; metastasis rare. Symptoms usually due to mass effect; occasionally carcinoid syndrome (5-HT secretion → flushing, diarrhea, wheezing).	Nests of neuroendocrine cells; chromogranin A ⊕.



A B C D

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A



B

FIGURE 2.15-10. Small cell lung cancer. Note the central location of the tumor in the PA **(A)** and lateral **(B)** CXRs. (Reproduced with permission from Kantarjian HM et al. MD Anderson Manual of Medical Oncology. New York, NY: McGraw-Hill; 2006.)

- **Adenocarcinoma:**
  - Most common lung cancer; **peripheral** location.
  - Includes **bronchoalveolar carcinoma,** associated with multiple nodules, interstitial infiltration, and prolific sputum production but is **not associated with smoking.**

TABLE 2.15-12. Paraneoplastic Syndromes of Lung Cancer

Classification	Syndrome	Histologic Type
Endocrine/ metabolic	Cushing syndrome (ACTH)	Small cell
	SIADH leading to hyponatremia	Small cell
	Hypercalcemia (PTHrP)	Squamous cell
	Gynecomastia	Large cell
Skeletal	Hypertrophic pulmonary osteoarthropathy (including digital clubbing)	Non–small cell
Neuromuscular	Peripheral neuropathy	Small cell
	Subacute cerebellar degeneration	Small cell
	Myasthenia (Lambert-Eaton syndrome)	Small cell
	Dermatomyositis	All
Cardiovascular	Migratory thrombophlebitis	Adenocarcinoma
	Nonbacterial verrucous endocarditis	Adenocarcinoma
Hematologic	Anemia	All
	DIC	All
	Eosinophilia	All
	Thrombocytosis	All
	Hypercoagulability	Adenocarcinoma
Cutaneous	Acanthosis nigricans	All

MNEMONIC

Lung cancer mets are often found in LABBs—

Liver
Adrenals
Brain
Bone

Q

A 25-year-old woman presents with dyspnea, chest pain, and leg pain. She takes birth control pills regularly. She returned from Asia 3 days ago. What is the next step?

- **SCC:** Has a **central** location; 98% are seen in smokers.
- **Large cell/neuroendocrine carcinomas:** Least common; associated with a poor prognosis.

History/Pe

- Presents with cough, hemoptysis, dyspnea, wheezing, pneumonia, chest pain, weight loss, and possible abnormalities on respiratory examination (crackles, atelectasis).
- **Horner syndrome** (miosis, ptosis, anhidrosis): Due to Pancoast tumor at the apex of the lung.
- **SVC syndrome:** Obstruction of the SVC with supraclavicular venous engorgement and facial swelling (see Figure 2.15-11).
- **Hoarseness:** 2° to recurrent laryngeal nerve involvement.
- Many **paraneoplastic syndromes** (see Table 2.15-12).



FIGURE 2.15-11. SVC syndrome. Prominent JVD is seen in SVC syndrome 2° to obstruction of the SVC by a central malignant lesion. (Reproduced with permission from Tintinalli JE et al. Tintinalli's Emergency Medicine: A Comprehensive Study Guide, 7th ed. New York, NY: McGraw-Hill; 2011.)

Diagnosis

- CXR or chest CT (initial test).
- Fine-needle aspiration (CT guided) for peripheral lesions; **bronchoscopy** (biopsy or brushing) for central lesions. These are the **definitive tests.**

Treatment

- **SCLC: Unresectable.** Often responds to radiation and chemotherapy initially but usually recurs; has a low median survival rate.
- **NSCLC: Surgical resection** in early stages. Supplement surgery with radiation or chemotherapy (depending on the stage). Palliative radiation and/or chemotherapy is appropriate for symptomatic but unresectable disease.

Pleural Disease

PLEURAL EFFUSION

An abnormal **accumulation of fluid in the pleural space.** Classified as follows:

- **Transudate:** 2° to ↑ pulmonary capillary wedge pressure (PCWP) or ↓ oncotic pressure.
- **Exudate:** 2° to ↑ pleural vascular permeability.

Table 2.15-13 lists the possible causes of both transudates and exudates.

TABLE 2.15-13. Causes of Pleural Effusion

Transudates	Exudates
CHF	Pneumonia (parapneumonic effusion
Cirrhosis	TB
Nephrotic syndrome	Malignancy
	PE
	Collagen vascular disease (rheumatoid arthritis, SLE)
	Pancreatitis
	Trauma

A

The next step is to treat with a heparin bolus. When there is high clinical suspicion (birth control, history of long flight, multiple symptoms) for a DVT, one should treat first and follow with imaging (CT angiogram). With patients who have lower clinical suspicion, imaging is warranted first prior to treatment.

History/PE

Presents with **dyspnea,** pleuritic chest pain, and/or cough. Examination reveals **dullness to percussion** and ↓ **breath sounds** over the effusion. A pleural friction rub may be present.

Diagnosis

- **CXR (initial test):** Costophrenic angle blunting. A lateral decubitus view can be used to assess loculation.
- **Thoracentesis:** Indicated for new effusions > 1 cm in decubitus view, except with bilateral effusions and other clinical evidence of CHF.
- The effusion is an exudate if it meets **any of Light's criteria** (see Table 2.15-14).

Treatment

- Directed toward the underlying condition causing the effusion.
- Complicated parapneumonic effusions and empyemas require **chest tube drainage** in addition to **antibiotic therapy** or **pleurodesis.**

KEY FACT

Complicated parapneumonic effusions necessitate chest tube drainage.

PNEUMOTHORAX

Collection of air in the pleural space that can lead to pulmonary collapse.

- **Etiologies:** Penetrating trauma, infection, and positive-pressure mechanical ventilation. Subtypes are as follows:
- **1° spontaneous pneumothorax:** 2° to rupture of subpleural apical blebs (usually found in **tall, thin young men**).
- **2° pneumothorax:** 2° to COPD, trauma, infections (TB, Pneumocystis jiroveci), and iatrogenic factors (thoracentesis, subclavian line placement, positive-pressure mechanical ventilation, bronchoscopy).
- **Tension pneumothorax:** A pulmonary or chest wall defect acts as a **one-way valve causing air trapping in the pleural space.** Buildup of air pushes the mediastinum to the **opposite** side of the chest, which can obstruct venous return to the heart, leading to **cardiac arrest** and **hemodynamic instability.** Shock and death unless immediately treated.

MNEMONIC

Presentation of pneumothorax—

P-THORAX

Pleuritic pain
Tracheal deviation
Hyperresonance
Onset sudden
Reduced breath sounds (and dyspnea)
Absent fremitus (asymmetric chest wall)
X-ray shows collapse

History/PE

- Presents with acute onset of unilateral pleuritic chest pain and dyspnea.
- Examination reveals tachypnea, diminished or absent breath sounds, hyperresonance, ↓ tactile fremitus, and JVD 2° to compression of the SVC.
- Tension pneumothorax also presents with respiratory distress, hypoxia, **tracheal deviation and hemodynamic instability.**

TABLE 2.15-14. Light's Criteria for Pleural Effusion [a]

Measure	Value
Pleural protein/serum protein	> 0.5
Pleural LDH/serum LDH	> 0.6
Pleural fluid LD	More than 2/3 the upper limit of normal serum LDH

[a]An effusion is an exudate if **any** of the above criteria are met.

Q

A 65-year-old with a 30-pack-year history presents with a 2-week history of facial swelling. Biopsy reveals a hilar small cell lung cancer (SCLC). What is the next step in treatment?

Diagnosis

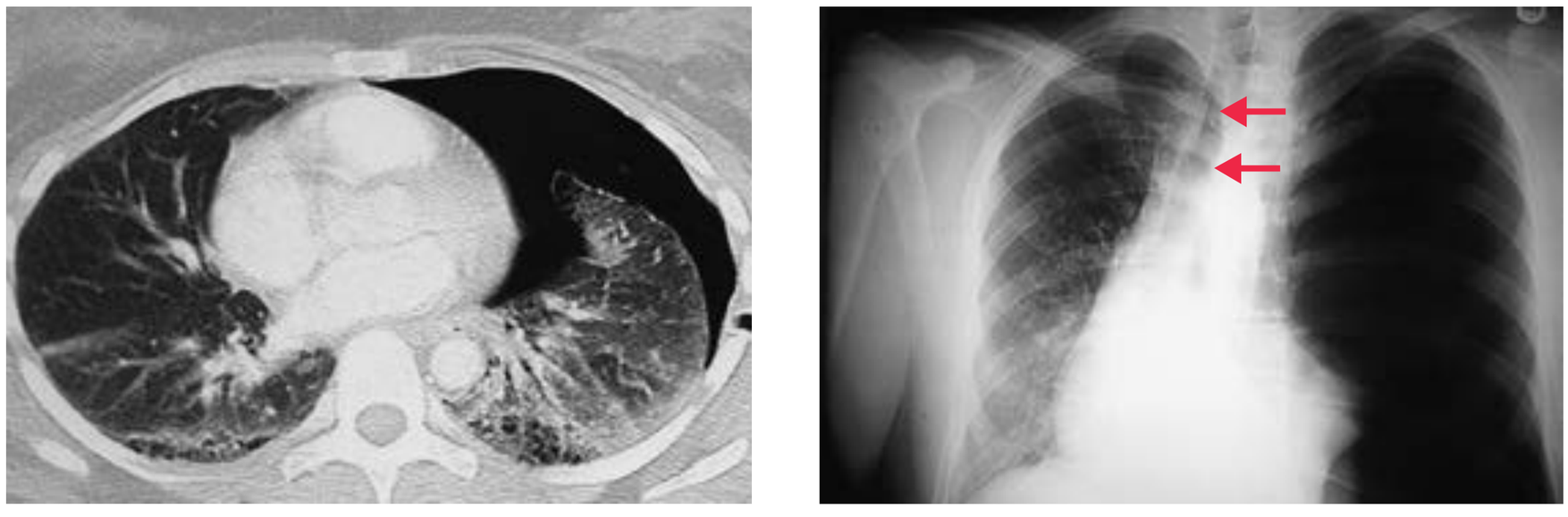
- The diagnosis of a **tension pneumothorax should be made clinically** and should be followed by immediate treatment.
- CXR shows the presence of a visceral pleural line and/or **lung retraction** from the chest wall (best seen in end-expiratory films; see Figure 2.15-12). Bedside ultrasound can also be used and has a high sensitivity and specificity.

Treatment

KEY FACT

Treatment of a tension pneumothorax requires needle decompression first, then chest tube placement

- Tension pneumothorax requires immediate needle decompression (second intercostal space at the midclavicular line) followed by chest tube placement.
- Small pneumothoraces may resorb spontaneously. Supplemental O_2 is helpful.
- Large, symptomatic pneumothoraces require chest tube placement.



A B

FIGURE 2.15-12. Pneumothorax. (A) Pneumothorax. CT shows collapsed left lung. **(B)** Tension pneumothorax. Note the hyperlucent left lung field with low left hemidiaphragm (below the field of view) and rightward mediastinal/tracheal shift. (Reproduced with permission from Le T et al. First Aid for the USMLE Step 1 2015. New York, NY: McGraw-Hill; 2015.)

A

The mainstay of therapy for SCLC is chemotherapy, which yields high rates of response.

HIGH-YIELD FACTS IN

RENAL/GENITOURINARY

Electrolyte Disorders 468
- Hypernatremia 468
- Hypo natremia 469
- Hyperkalemia 470
- Hypo kalemia 471
- Hyperc alc emia 472
- Hypo c alc emia 473
- Hypo magnesemia 473

Acid-Base Disorders 474

Renal Tubular Acidosis 474

Acute Kidney Injury 474

Chronic Kidney Disease 475

Diuretics 477

Glomerular Disease 477
- Nephritic Syndrome 477
- Nephrotic Syndrome 478

Nephrolithiasis 481

Polycystic Kidney Disease 485

Hydronephrosis 486

Scrotal Swelling 486

Erectile Dysfunction 487

Benign Prostatic Hyperplasia 488

Prostate Cancer 489

Bladder Cancer 490

Renal Cell Carcinoma 491

Testicular Cancer 492

Electrolyte Disorders

HYPERNATREMIA

KEY FACT

Certain patients (eg, infants, intubated patients, those with a change in mental status) may not drink enough free water to replace insensible losses. This can cause or worsen hypernatremia.

Serum sodium > 145 mEq/L. Usually due to **free water loss** rather than sodium gain. Refer to the Endocrinology chapter for a review of **diabetes insipidus,** an important cause of hypernatremia.

History/Pe

Presents with **thirst** (due to hypertonicity), **neurologic symptoms** including mental status changes, weakness, focal neurologic deficits, hyporeflexia, and seizures.

Diagnosis

See Figure 2.16-1 for the hypernatremia diagnostic algorithm. Diagnosis based on **urine osmolality and urine sodium.**

MNEMONIC

Hypernatremia causes—

The 6 D's

Diuresis
Dehydration
Diabetes insipidus (DI)
Docs (iatrogenic)
Diarrhea
Disease (eg, kidney, sickle cell)

Treatment

- Determine volume status. If hypovolemic **with unstable vital signs, use isotonic 0.9% NaCl** before correcting free water deficits. If normal VS and asymptomatic, can treat with D_5W.
- Determine free water deficit. **Water deficit** = Total body water × ([serum Na / 140] – 1).
  - Total body water (TBW) is ~ 60% of lean body weight.
  - Replace with **D_5W,** 0.45% NaCl, or enteral water.
- **Determine rate of replacement.** Correction of chronic hypernatremia (> 48 hours) should be accomplished **gradually over 48–72 hours** (≤ 0.5 mEq/L/hr) to prevent neurologic damage 2° to cerebral edema.
- Euvolemic and hypervolemic hypernatremia are rare and treated with a combination of diuretics and D_5W to remove excess Na.

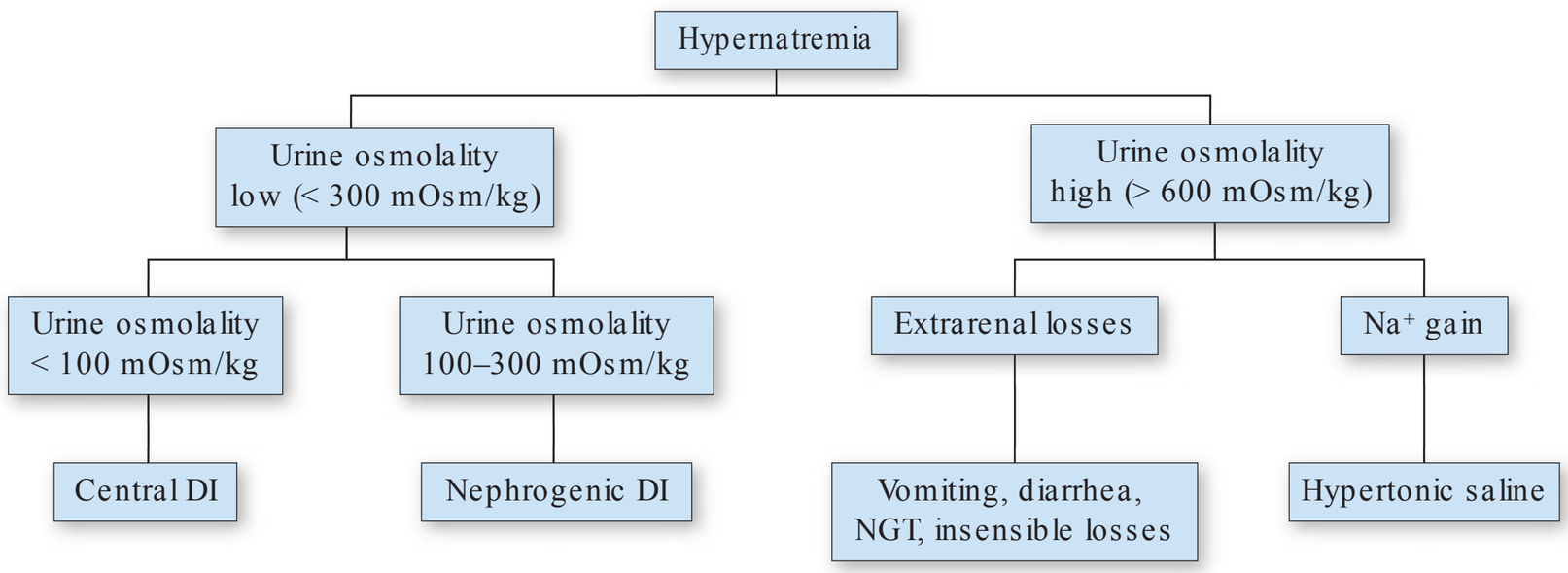


FIGURE 2.16-1. Diagnostic algorithm for hypernatremia. Diagnosis of central DI and nephrogenic DI also established by use of the DDAVP replacement test (see Endocrinology chapter). Intermediate values (300–600 mOsm/kg) often due to osmotic diuresis, though can occasionally be seen in DI. Urine sodium measurement can also be helpful to distinguish extrarenal losses (urine sodium < 25 mEq/L) from sodium gain (> 100 mEq/L). DI = diabetes insipidus, NGT = nasogastric tube.

HYPONATREMIA

Serum sodium < 135 mEq/L. Almost always due to ↑ ADH.

History/Pe

- May be asymptomatic or may present with **confusion, lethargy,** muscle cramps, hyporeflexia, and nausea.
- Can progress to seizures, coma, or brainstem herniation.

Diagnosis

Calculate serum osmolality (S_{osm}) as the first step in evaluation: S_{osm} = (2 × serum Na) + (BUN/2.8) + (glucose/18). Hypotonic hyponatremia is the most common and is further categorized by volume status. See Figure 2.16-2 for the full diagnostic algorithm.

Treatment

- Treat underlying disorder. Treat hypervolemic and euvolemic etiologies with **water restriction** ± diuretics. If **hypovolemic,** replete volume with **NS.** If severe hyponatremia (Na < 120 mEq/L), consider hypertonic saline.
- Chronic hyponatremia (> 72 hours' duration) should be corrected slowly (< 8 mEq/L/day) in order to prevent central pontine myelinolysis or osmotic demyelination (symptoms include paraparesis/quadriparesis, dysarthria, and coma). See Figure 2.16-3.

KEY FACT

Consider using hypertonic saline only if a patient has seizures due to hyponatremia, and when serum Na^+ is < 120 mEq/L. In most cases, NS is the best replacement fluid.

KEY FACT

Correcting hyponatremia too rapidly can lead to **central pontine myelinolysis.**

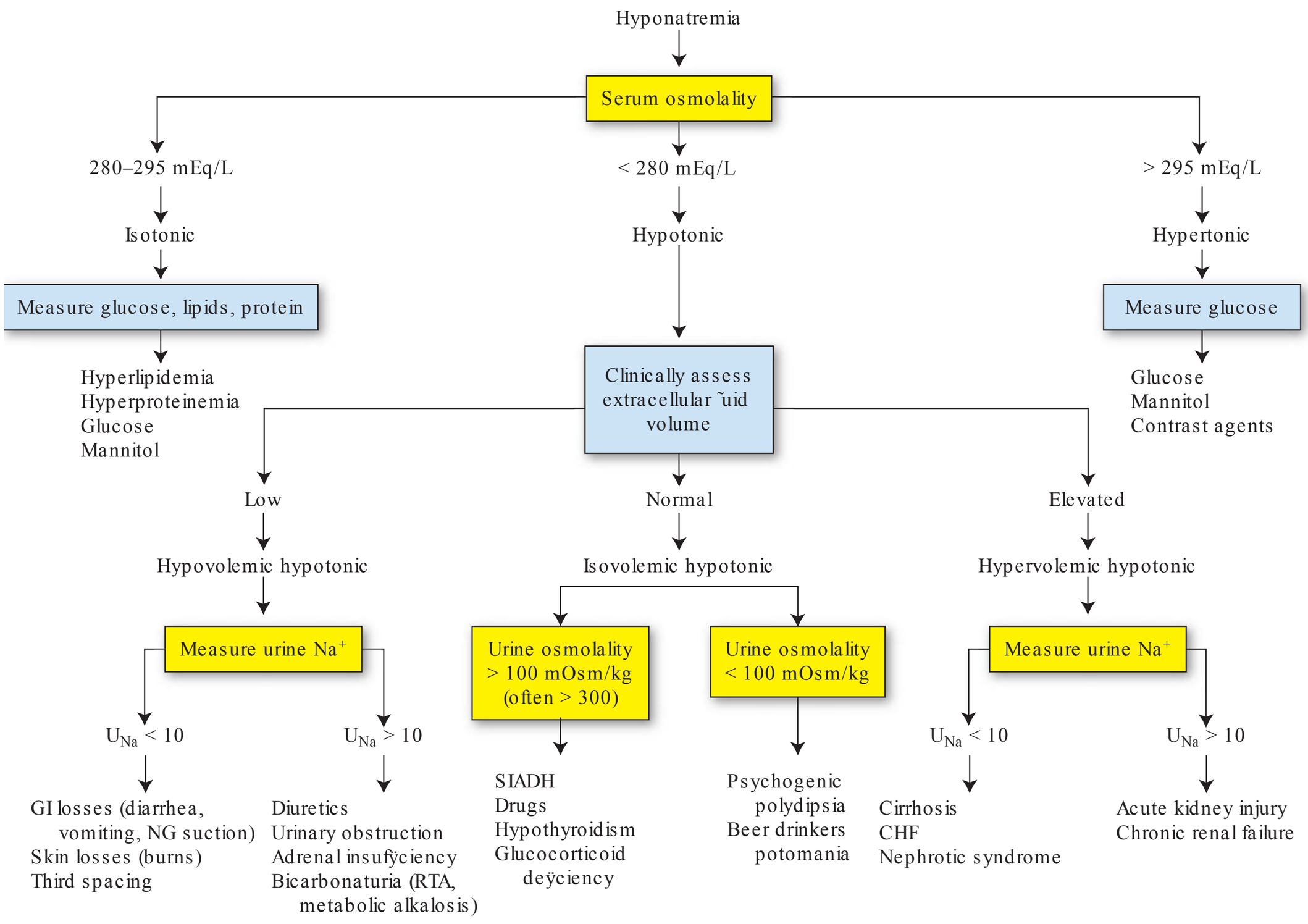


FIGURE 2.16-2. Diagnostic algorithm for hyponatremia. Boxes highlighted in yellow represent key lab tests to perform.

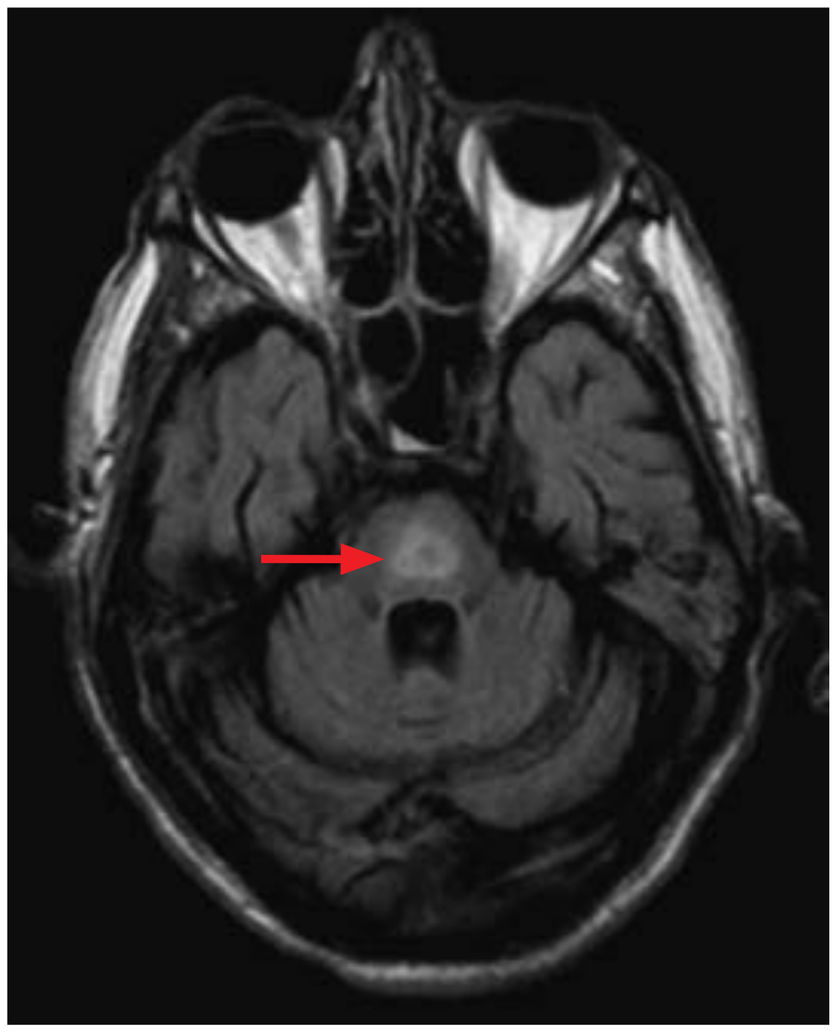


FIGURE 2.16-3. Central pontine myelinolysis on MRI. (Used with permission from Dr. Frank Gaillard.)

HYPERKALEMIA

Serum potassium > 5 mEq/L. Etiologies are as follows:

- **Spurious:** Hemolysis of blood samples, fist clenching during blood draws, delays in sample analysis, extreme leukocytosis or thrombocytosis.
- **↓ excretion:** Renal insufficiency, drugs (eg, spironolactone, triamterene, amiloride, ACEIs, trimethoprim, NSAIDs), hypoaldosteronism, type IV renal tubular acidosis (RTA), calcineurin inhibitors.
- **Cellular shifts:** Cell lysis, tissue injury **(rhabdomyolysis), tumor lysis syndrome,** insulin deficiency, acidosis, drugs (eg, succinylcholine, digitalis, arginine, **β-blockers**), exercise, resorption of blood (hematomas, GI bleeding).
- **Increase intake:** Food (most fruits, potatoes), iatrogenic.

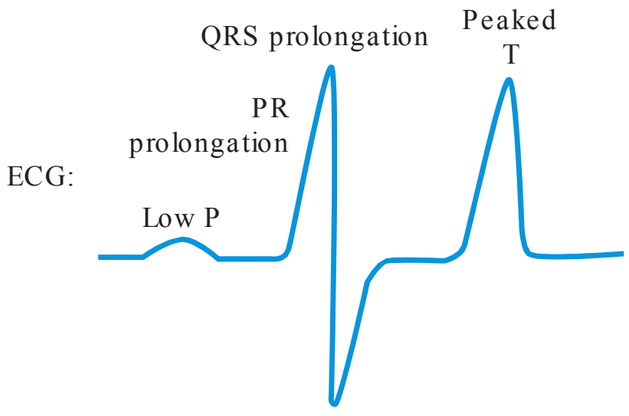


FIGURE 2.16-4. Hyperkalemia on ECG. Electrocardiographic manifestations include peaked T waves, PR prolongation, and a widened QRS complex. (Reproduced with permission from Cogan MG. Fluid and Electrolytes. Stamford, CT: Appleton & Lange; 1991.)

History/Pe

May be asymptomatic or may present with nausea, vomiting, **intestinal colic, areflexia, weakness,** flaccid paralysis, arrhythmias, and paresthesias.

Diagnosis

- Confirm hyperkalemia with a **repeat blood draw.** In the setting of extreme leukocytosis or thrombocytosis, check plasma potassium.
- Other workup: **Do an ECG** to evaluate for cardiac complications. ECG findings include **tall, peaked T waves;** a wide QRS; PR prolongation; and loss of P waves (see Figure 2.16-4). Can progress to **sine waves,** ventricular fibrillation, and cardiac arrest.

Treatment

- Values > 6.5 mEq/L or ECG changes (especially PR prolongation or wide QRS) require emergent treatment.

- The mnemonic **C BIG K** and the steps listed below summarize the treatment of hyperkalemia.
  - The first step is always to give **calcium gluconate** for cardiac cell membrane stabilization. **Needed only if potassium > 6.5 mEq/L or ECG changes.**
  - Give **bicarbonate and/or insulin and glucose** to temporarily shift potassium into cells. **Most rapid** way to shift K^+ into cells.
  - β-agonists (eg, albuterol) promote cellular reuptake of potassium.
  - Eliminate potassium from diet and IV fluids.
  - **Kayexalate (sodium polystyrene sulfonate)** to remove potassium from the body. Contraindications include ileus, bowel obstruction, ischemic gut, or pancreatic transplants (can cause bowel necrosis).
- Loop diuretics can be used for increasing urinary excretion of potassium.
- Dialysis is appropriate for patients with renal failure or for severe, refractory cases.

HYPOKALEMIA

Serum potassium < 3.6 mEq/L. Etiologies are as follows:

- **Transcellular shifts:** Insulin, β_2-agonists, and alkalosis all cause potassium to shift intracellularly (see Figure 2.16-5).
- **GI losses:** Diarrhea, chronic laxative abuse, vomiting, NG suction.
- **Renal losses: Diuretics** (eg, loop or thiazide), 1° mineralocorticoid excess or 2° hyperaldosteronism, ↓ circulating volume, Bartter and Gitelman syndromes, drugs (eg, gentamicin, amphotericin), DKA, **hypomagnesemia,** type I and type II RTA, polyuria.

History/Pe

Presents with fatigue, **muscle weakness or cramps, ileus,** hyporeflexia, paresthesias, rhabdomyolysis, and ascending paralysis.

Diagnosis

- Serum potassium levels.
- May distinguish renal from GI losses with 24-hour or spot urine potassium.
- Other workup: **ECG** may show **T-wave flattening, U waves** (an additional wave after the T wave), and ST-segment depression, leading to AV block and subsequent cardiac arrest. See Figure 2.16-6.

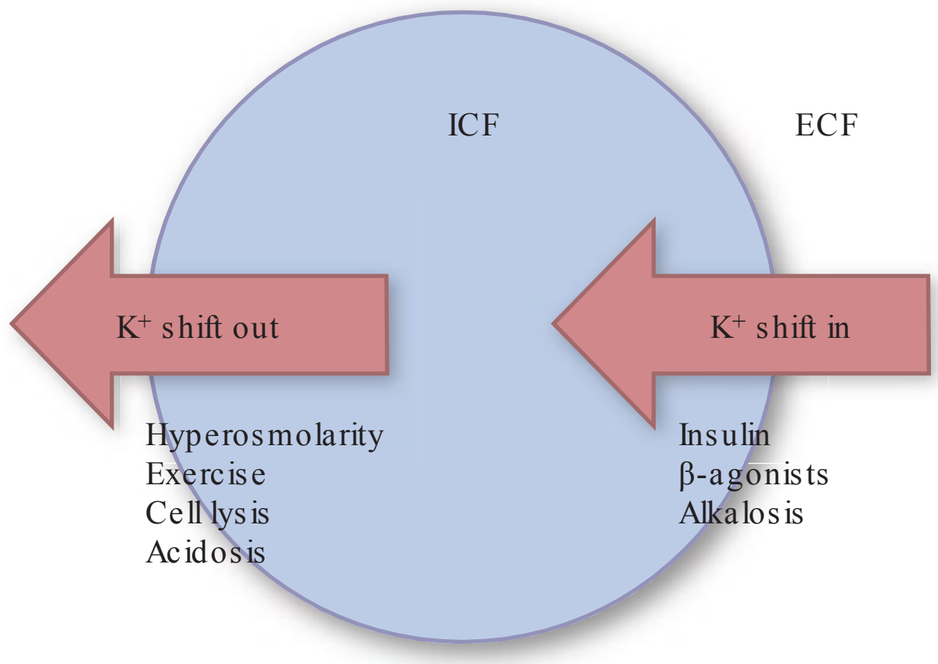


FIGURE 2.16-5. Causes of transcellular potassium shifts.

MNEMONIC

Treatment of hyperkalemia—

C BIG K

Calcium
Bicarbonate, **B**eta-2 agonists
Insulin + **G**lucose
Kayexalate (sodium polystyrene sulfonate)

KEY FACT

Patients with metabolic alkalosis, hypokalemia, and a normal BP probably have one of the following conditions:

- Surreptitious vomiting
- Diuretic abuse
- Bartter syndrome (transport defect in thick ascending limb)
- Gitelman syndrome (transport defect in the distal convoluted tubule)

KEY FACT

Hypokalemia is usually due to renal or GI losses.

KEY FACT

If a patient is on digitalis, **potassium** levels must be carefully monitored. Hypokalemia sensitizes the heart to digitalis toxicity, because K^+ and digitalis compete for the same sites on the Na^+/K^+ pump.

Q

A 29-year-old woman with a history of bipolar disorder presents to the ED with altered mental status. On exam she has dry mucous membranes and ↓ skin turgor with a BP of 92/40 mm Hg and HR of 106 bpm. Her serum sodium level comes back at 154 mEq/L. What is the next best step in management?



FIGURE 2.16-6. Hypokalemia on ECG. Prominent U wave indicated by arrow. (Reproduced with permission from Van Beers EJ, Stam J, van den Bergh WM. Licorice consumption as a cause of posterior reversible encephalopathy syndrome: a case report. Crit Care. 2011;15(1):R64.)

KEY FACT

If hypokalemia is not responding to potassium repletion, **check magnesium levels.**

MNEMONIC

Causes of hypercalcemia—

CHIMPANZEES

Calcium supplementation
Hyperparathyroidism/**H**yperthyroidism
Iatrogenic (eg, thiazides, parenteral nutrition)/**I**mmobility (especially in the ICU setting)
Milk-alkali syndrome
Paget disease
Adrenal insufficie y/**A**cromegaly
Neoplasm
Zollinger-Ellison syndrome (eg, MEN type 1)
Excess vitamin A
Excess vitamin D
Sarcoidosis and other granulomatous disease

KEY FACT

Loops (furosemide) **L**ose calcium.

A

This patient probably has nephrogenic DI from presumed lithium use. She is hypovolemic with unstable vital signs; therefore, she should be treated initially with NS and switched to D_5W once her volume status improves.

Treatment

- Treat the underlying disorder.
- Oral and/or IV **potassium repletion.** Do not exceed 20 mEq/L/hr.
- Replace **magnesium,** as this deficiency makes potassium repletion more difficult.

HYPERCALCEMIA

Serum calcium > 10.2 mg/dL (corrected for serum albumin). The most common causes are **hyperparathyroidism and malignancy** (eg, breast cancer, squamous cell carcinoma, multiple myeloma). Other causes are summarized in the mnemonic **CHIMPANZEES.**

History/Pe

Usually asymptomatic but can present with **bones** (osteopenia, fractures), **stones** (kidney stones), abdominal **groans** (anorexia, constipation), and **psychiatric overtones** (weakness, fatigue, altered mental status).

Diagnosis

- Order a total/ionized calcium, albumin, phosphate, PTH.
- Other workup: parathyroid hormone–related peptide (PTHrP) if malignancy suspected, serum protein electrophoresis for multiple myeloma, vitamin D if granulomatous disease (sarcoid, TB) suspected, and ECG (may show a **short QT interval**).

Treatment

- **IV hydration.**
- If serum calcium >14 mg/dL, treat with IV fluids and calcitonin, bisphosphonates (eg, zoledronic acid, pamidronate).
- **Avoid thiazide diuretics,** which ↑ tubular reabsorption of calcium.
- **Steroids for granulomatous diseases.**

HYPOCALCEMIA

Serum calcium < 8.5 mg/dL. Etiologies include hypoparathyroidism (**post-surgical,** idiopathic), secondary hyperparathyroidism (CKD), malnutrition, hypomagnesemia, acute pancreatitis, vitamin D deficiency, chelation from **citrate** found in blood products, and pseudohypoparathyroidism. In infants, consider DiGeorge syndrome.

History/PE

- Presents with **abdominal muscle cramps,** dyspnea, **tetany, perioral and acral paresthesias (classic symptoms in the transient hypocalcemia in hyperventilation),** and convulsions.
- Facial spasm elicited from tapping of the facial nerve **(Chvostek sign)** and carpal spasm after arterial occlusion by a BP cuff **(Trousseau sign)** are classic findings that are most commonly seen in severe hypocalcemia.

Diagnosis

- **Ionized Ca^{2+} and PTH** are the most useful tests in the diagnosis. See Endocrinology chapter for interpretation of PTH levels.
- If the patient has had a thyroidectomy, review the operative note to determine if there was any potential damage to the parathyroid glands.
- Mg^{2+} (if low can induce PTH resistance), albumin, 25-OH vitamin D, and 1,25-OH vitamin D levels may also be helpful depending on clinical situation.
- Other workup: ECG may show a **prolonged QT interval.**

Treatment

- Treat the underlying disorder.
- Magnesium repletion.
- Administer oral **calcium supplements;** give oral and IV calcium for severe symptoms.

HYPOMAGNESEMIA

Serum magnesium < 1.5 mEq/L. Etiologies are as follows:

- ↓ **intake:** Malnutrition, malabsorption, short bowel syndrome, TPN, PPIs.
- ↑ **loss:** Diuretics, diarrhea, vomiting, hypercalcemia, **alcoholism.**
- **Miscellaneous: DKA,** pancreatitis, extracellular fluid volume expansion.

History/PE

In severe cases, symptoms may include hyperactive reflexes, tetany, paresthesias, irritability, confusion, lethargy, seizures, and arrhythmias.

Diagnosis

- Lab results may show concurrent hypocalcemia and hypokalemia.
- ECG may reveal prolonged PR and QT intervals.

Treatment

- IV and oral supplements.
- **Hypokalemia and hypocalcemia will not correct without magnesium correction.**

KEY FACT

A classic case of hypocalcemia is a patient who develops cramps and tetany following thyroidectomy.

KEY FACT

Serum calcium levels may be falsely low in hypoalbuminemia; check ionized calcium. Corrected Ca^{2+} = Total serum Ca^{2+} + 0.8 (4 – serum albumin).

KEY FACT

Alcoholics are the most common patient population with hypomagnesemia.

KEY FACT

ASA (salicylate) overdose can cause both a metabolic acidosis and a respiratory alkalosis.

MNEMONIC

Specific treatments for anion-gap causes of metabolic acidosis*—

MUDPILES

Methanol: Fomepizole
Uremia: Dialysis
DKA: Insulin, fluid
Paraldehyde, **P**henformin
Iron, **I**NH: GI lavage, charcoal (INH)
Lactic acidosis: IVF
Ethylene glycol: Fomepizole
Salicylates: Alkalinize urine

*Sodium bicarbonate used only in severe acidosis (pH < 7.2).

KEY FACT

Ethylene glycol presentation = Urine calcium oxalate (envelope-shaped) crystals.
Methanol presentation = Vision loss, optic disc hyperemia.

Acid-Base Disorders

See Figure 2.16-7 for a diagnostic algorithm of acid-base disorders.

Renal Tubular Acidosis

A net ↓ in either tubular H^+ secretion or HCO_3^- reabsorption that leads to a **non-anion-gap metabolic acidosis.** There are three main types of RTA; **type IV (distal)** is the **most common form** (see Table 2.16-1).

KEY FACT

AKI and toxin exposure in the history should lead you to a diagnosis of ATN.

Acute Kidney Injury

Formerly known as **acute renal failure.** Defined as an abrupt ↓ in renal function leading to the retention of creatinine and BUN. ↓ urine output (oliguria, defined as < 500 mL/day) is not required for acute kidney injury. Complications include metabolic acidosis, electrolyte abnormalities, and volume overload; ultimately may progress to CKD. See Table 2.16-2 for the workup of AKI.

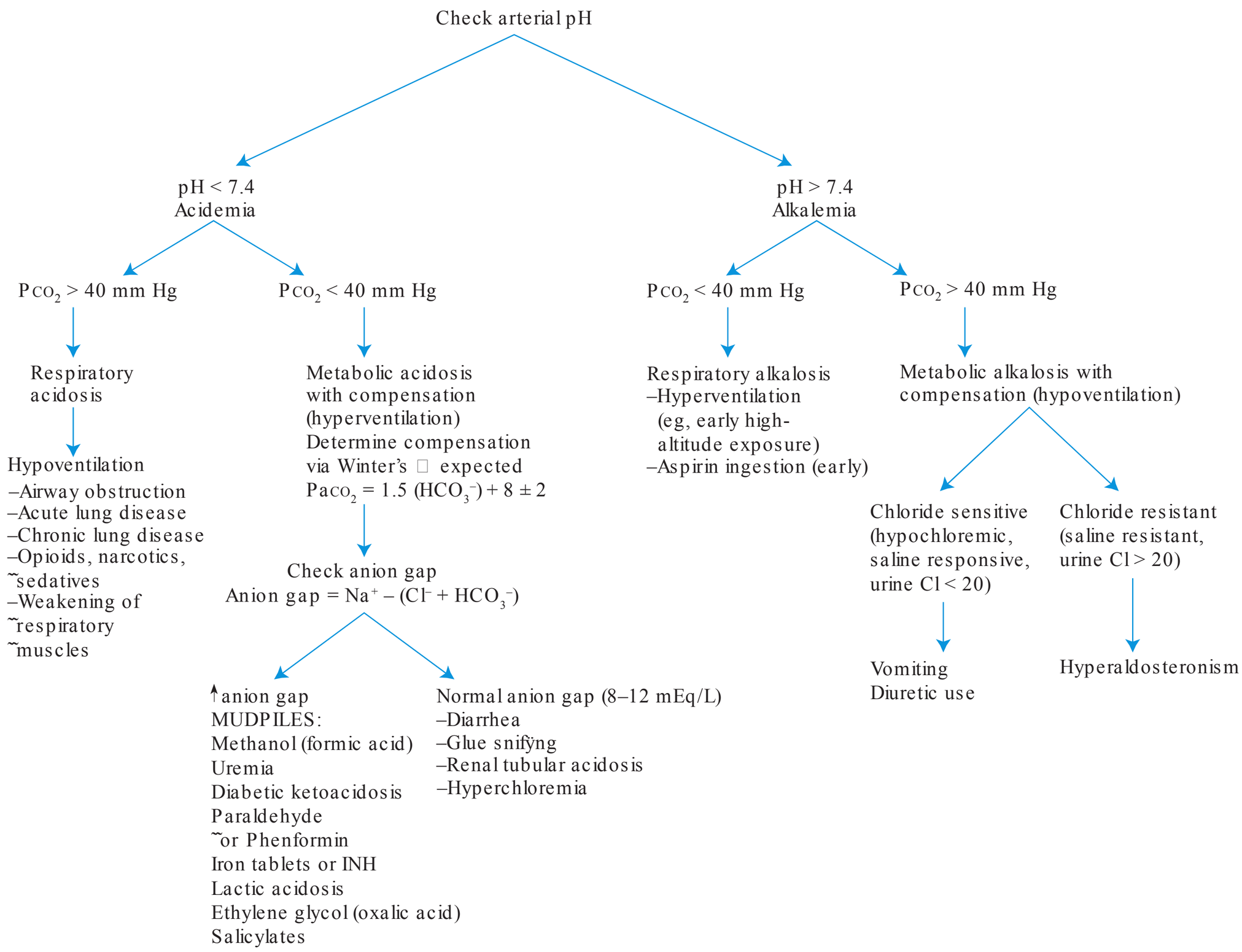


FIGURE 2.16-7. Diagnostic algorithm for acid-base disorders.

TABLE 2.16-1. Types of RTA

Variable	type i (distal)	type ii (proximal)	type iV (distal)
Defect	H^+ secretion.	HCO_3^- reabsorption.	Aldosterone deficiency or resistance.
Serum K^+	Low.	Low.	**High.**
Urinary pH	> 5.3	5.3 initially; < 5.3 once serum is acidic.	< 5.3
Etiologies (most common)	**Autoimmune disorders,** hypercalciuria, ifosfamide.	**Multiple myeloma,** amyloidosis, Fanconi, cystinosis, ifosfamide.	Hyporeninemic hypoaldosteronism (eg, renal insufficiency), angiotensin II inhibition (ACEIs/ARBs), heparin.
Treatment	Replace bicarbonate.	Thiazides, volume depletion to increase reabsorption of bicarbonate.	Furosemide, mineralocorticoid replacement.
Complications	**Nephrolithiasis.**	Rickets, osteomalacia.	

Chronic Kidney Disease

Defined as **> 3 months** of GFR < 60 mL/min **or** kidney damage (structural/functional abnormalities). Most commonly due to **diabetes mellitus (DM), hypertension,** and glomerulonephritis. Another commonly tested etiology is polycystic kidney disease (PKD).

History/Pe

Generally asymptomatic until GFR is < 30 mL/min, but patients gradually experience the signs and symptoms of uremia (anorexia, nausea, vomiting, uremic pericarditis, "uremic frost," delirium, seizures, coma).

Diagnosis

Common metabolic derangements include the following:

- Azotemia (↑ BUN and creatinine).
- Fluid retention (hypertension, edema, CHF, pulmonary edema).
- Metabolic acidosis.
- Hyperkalemia.
- Anemia (↓ erythropoietin production).
- Abnormal hemostasis caused by impaired platelet aggregation.
- Hypocalcemia, hyperphosphatemia, 2° hyperparathyroidism (↓ phosphate excretion; impaired vitamin D production leading to renal osteodystrophy).
- Microscopic urine examination with broad, waxy casts.

Treatment

- ACEIs/ARBs and hypertension control have been shown to ↓ the progression of CKD.
- Use **desmopressin (DDAVP) in cases of abnormal bleeding.**
- Erythropoietin analogues for anemia of chronic disease.
- Fluid restriction; ↓ Na^+/K^+/phosphate intake.
- Oral phosphate binders (calcium acetate, calcium carbonate, sevelamer, lanthanum) and calcitriol (1,25-OH vitamin D) for renal osteodystrophy.
- **Renal replacement therapy** includes hemodialysis, peritoneal dialysis, and renal transplantation.

MNEMONIC

Indications for urgent dialysis—

AEIOU

Acidosis
Electrolyte abnormalities (hyperkalemia)
Ingestions (salicylates, theophylline, methanol, barbiturates, lithium, ethylene glycol)
Overload (fluid
Uremic symptoms (pericarditis, encephalopathy, bleeding, nausea, pruritus, myoclonus)

KEY FACT

Do not give metformin to septic patients or those with renal or hepatic failure, because it can worsen the metabolic acidosis.

TABLE 2.16-2. Acute Kidney Injury

	Prerenal	Intrinsic	Postrenal
Pathophysiology	Decreased renal perfusion.	Injury within the nephron.	Urinary outflow obstruction.
Common etiologies	**Hypovolemia,** shock, decreased intravascular volume (cirrhosis, nephrotic syndrome), renal artery stenosis, hepatorenal syndrome, drugs **(NSAIDs, ACEIs),** CHF.	**ATN** from ischemia or toxins, AIN, glomerulonephritis, embolic disease, rhabdomyolysis.	**Prostatic disease,** pelvic tumors, intratubular obstruction from crystalluria (acyclovir), bilateral stones.
History/PE	Symptoms of hypovolemia (tachycardia, hypotension) or other underlying disease process (liver failure, nephrotic syndrome).	Hx of drug exposure (aminoglycosides, NSAIDs, penicillins), **contrast media.** Creatinine spikes in **5–10 days** with drug injuries, **24 hours** with contrast injuries.	Decreased urine output, suprapubic pain, distended bladder, bladder scan shows **postvoid residual > 50 mL.**
		Lab Values	
BUN/Creatinine ratio	> 20:1	< 15:1	Varies.
Fractional excretion of sodium (Fe_{Na})	< 1%	> 2%	> 1–2%
Urine sodium	< 20 mEq/L	> 40 mEq/L	> 40 mEq/L
Urine Osms	> 500 mOsm/kg	< 350 mOsm/kg (isosthenuria, damaged tubules cannot reabsorb water).	< 350 mOsm/kg
Urine sediment	Hyaline casts (normal finding, but ↑ in volume depletion).	RBC casts/dysmorphic RBCs (glomerulonephritis), WBCs/**eosinophils** (AIN), "muddy-brown cast" (ATN) (see Figure 2.16-8), WBC casts (pyelonephritis), fatty casts (nephrotic syndrome).	
Treatment	Fluids. Avoid nephrotoxic drugs (metformin, NSAIDs). For all etiologies, dialyze if meet **AEIOU** criteria (see mnemonic).	Prevent contrast nephropathy with **IVF** or nonionic contrast agents. Discontinue offending medications.	Bladder catheterization.

Complications

Acquired **renal cystic disease** in patients undergoing long-term dialysis. **Cardiovascular complications (MI, sudden cardiac death)** are the most common cause of death.

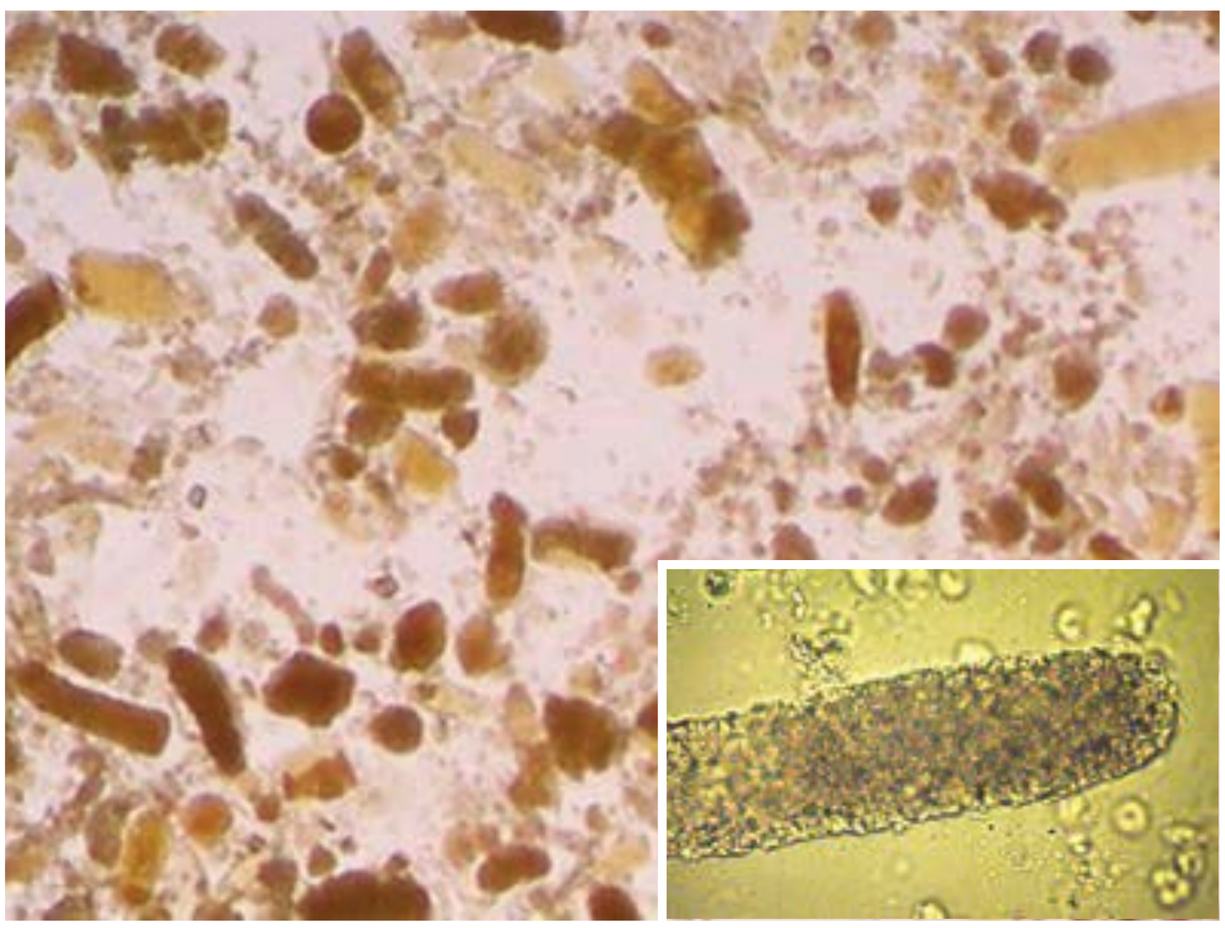


FIGURE 2.16-8. Findings on microscopic urine examination in AKI. "Muddy brown casts." (Reproduced with permission from Dr. Serban Nicolescu.)

Diuretics

Table 2.16-3 summarizes the mechanisms of action and side effects of commonly used diuretics. Figure 2.16-9 provides a review of nephron physiology with diuretic sites of action.

Glomerular Disease

NEPHRITIC SYNDROME

A disorder of glomerular inflammation, also called glomerulonephritis. Proteinuria may be present but is usually < 1.5 g/day. Causes are summarized in Table 2.16-4.

History/Pe

The classic findings are oliguria, macroscopic/microscopic hematuria (tea- or cola-colored urine), hypertension, and **edema (can also present with pulmonary edema).**

Diagnosis

- UA shows hematuria and possibly mild proteinuria.
- Patients have a ↓ GFR with elevated BUN and creatinine. See Table 2.16-4 for pertinent labs.
- Renal biopsy may be useful for histologic evaluation.
- Findings are shown in Figure 2.16-10.

KEY FACT

Postinfectious glomerulonephritis will present **2–6 weeks** after an infection and has a **low C3;** IgA nephropathy will present a **few days** after an infection and has a **normal C3.**

KEY FACT

Granulomatosis with polyangiitis = kidney + lung + sinus.
Microscopic polyangiitis = kidney + lung.
Churg-Strauss = kidney + asthma.

MNEMONIC

Nephritic syndrome finding —

PHAROH

Proteinuria
Hematuria
Azotemia
RBC casts
Oliguria
Hypertension

TABLE 2.16-3. Mechanism of Action and Side Effects of Diuretics

Type	Drugs	Site of Action	Mechanism of Action	Side Effects
Carbonic anhydrase inhibitors	Acetazolamide.	Proximal convoluted tubule.	Inhibit carbonic anhydrase, ↑ H^+ reabsorption, block Na^+/H^+ exchange.	Hyperchloremic metabolic acidosis, sulfa allergy.
Osmotic agents	Mannitol, urea.	Entire tubule.	↑ tubular fluid osmolarity.	Pulmonary edema due to CHF and anuria.
Loop agents	Furosemide, ethacrynic acid, bumetanide, torsemide.	Ascending loop of Henle.	Inhibit $Na^+/K^+/2Cl^-$ transporter.	Water loss, metabolic alkalosis, ↓ K^+, ↓ Ca^{2+}, ↓ Mg^+, ototoxicity, sulfa allergy (except ethacrynic acid), hyperuricemia.
Thiazide agents	HCTZ, chlorothiazide.	Distal convoluted tubule.	Inhibit Na^+/Cl^- transporter.	Water loss, metabolic alkalosis, ↓ **Na^+**, ↓ **K^+**, ↑ glucose, ↑ **Ca^{2+}**, ↑ uric acid, sulfa allergy, pancreatitis.
K^+-sparing agents	Spironolactone, triamterene, amiloride.	Cortical collecting tubule.	Aldosterone receptor antagonist (spironolactone); block sodium channel (triamterene, amiloride).	Metabolic acidosis; ↑ K^+; antiandrogenic effects, including gynecomastia (spironolactone).

KEY FACT

Differential dx for nephritic/nephrotic syndrome with **low C3:** postinfectious, membranoproliferative glomerulonephritis (including mixed cryoglobulinemia), and lupus nephritis.

KEY FACT

Mixed cryoglobulinemia presents with palpable purpura, arthralgias, nephritic/nephrotic syndrome, **low C3,** and positive **HCV.**

Treatment

- Treat hypertension, fluid overload, and uremia with salt and water restriction, diuretics, and, if necessary, dialysis.
- In some cases, **corticosteroids** are useful in reducing glomerular inflammation.

NEPHROTIC SYNDROME

Defined as **proteinuria (≥ 3.5 g/day), generalized edema, hypoalbuminemia,** and **hyperlipidemia.** Approximately one-third of all cases result from systemic diseases such as DM, SLE, or amyloidosis. Causes are summarized in Table 2.16-5. Findings are shown in Figure 2.16-11.

History/Pe

- Presents with **generalized edema** and **foamy urine.** In severe cases, dyspnea and ascites may develop.
- Patients have ↑ susceptibility to infection as well as **hypercoagulable** states with an ↑ **risk of venous thrombosis** and pulmonary embolism (due to loss of antithrombin 3, increased platelet aggregation, and changes in protein C and S levels).

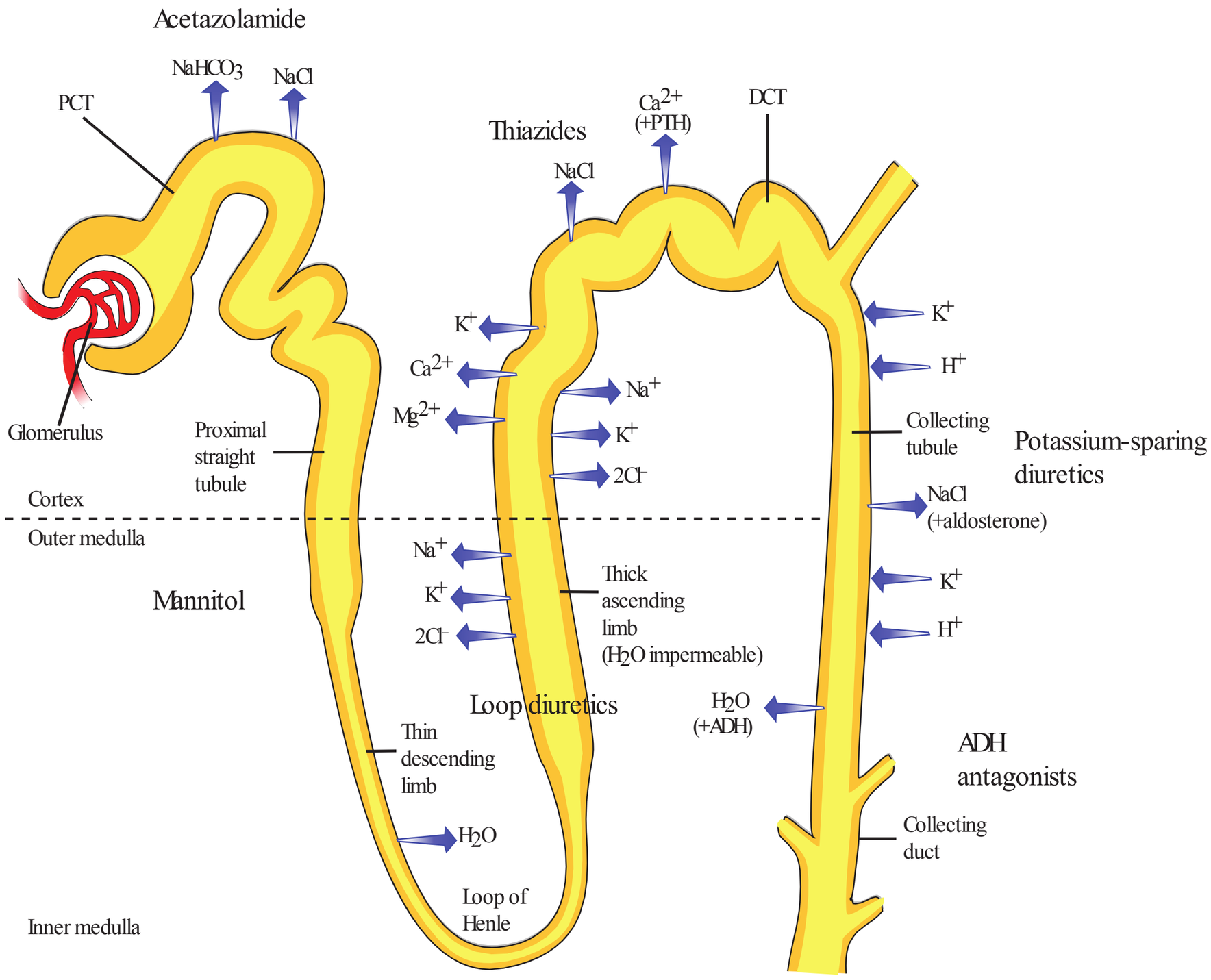


FIGURE 2.16-9. Diuretics: Site of action. (Adapted with permission from Katzung BG, Trevor AJ. Basic and Clinical Pharmacology, 13th ed. New York, NY: McGraw-Hill; 2015.)

TABLE 2.16-4. Causes of Nephritic Syndrome

disorder	description	history/pe	labs/histology	treatment/prognosis
		immune complex		
Postinfectious glomerulonephritis	Classically associated with recent group A β-hemolytic **streptococcal infection,** but can be seen with any infection (usually 2–6 weeks prior).	Oliguria, edema, hypertension, tea- or cola-colored urine.	**Low serum C3** that normalizes 6–8 weeks after presentation; **↑ ASO and anti-DNase titers; lumpy-bumpy immunofluo escence.**	Supportive with diuretics to prevent fluid verload. Most patients have a complete recovery.
IgA nephropathy (Berger disease)	The most common type; **typically follows upper respiratory or GI infections.** Commonly seen in young men; associated with Henoch-Schönlein purpura.	Episodic gross hematuria or persistent microscopic hematuria.	**Normal C3.**	Glucocorticoids for select patients; ACEIs in patients with proteinuria. Some 20% of cases progress to ESRD.

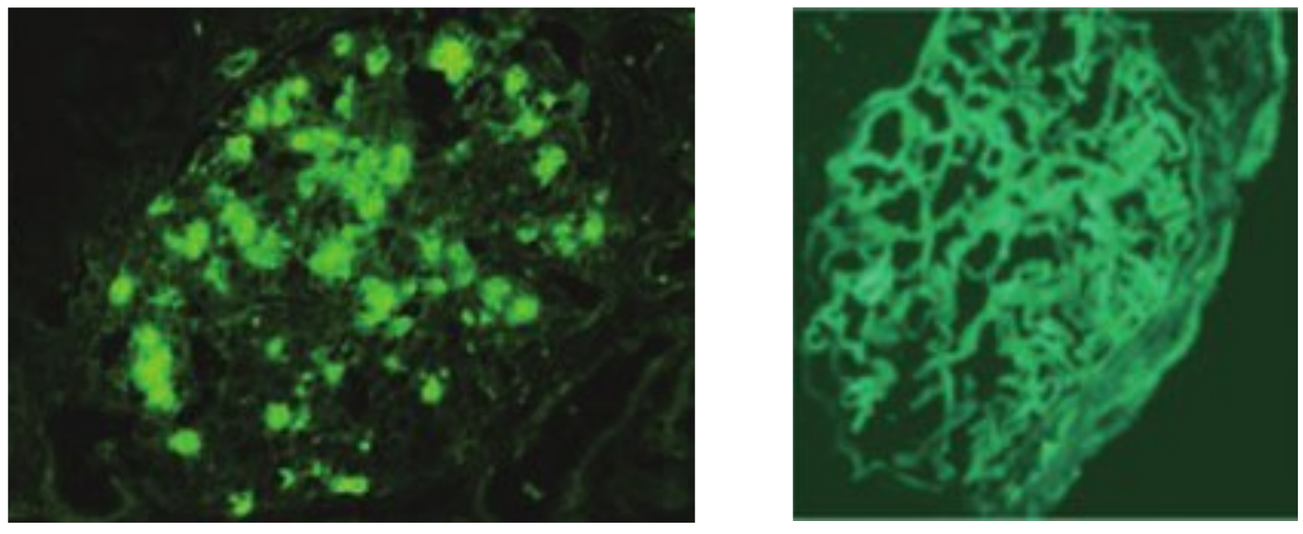
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TABLE 2.16-4. Causes of Nephritic Syndrome (continued)

Disorder	Description	History/PE	Labs/Histology	Treatment/Prognosis
		IMMUNE COMPLEX		
Henoch-Schönlein purpura	Small vessel vasculitis, often seen in childhood.	Triad: **Palpable purpura, arthralgias, abdominal pain.**	Identical to IgA nephropathy.	Supportive therapy ± glucocorticoids.
		PAUCI-IMMUNE (NO IG DEPOSITS ON IMMUNOFLUORESCENCE)		
GPA (formerly Wegener granulomatosis)	Granulomatous inflammation of the respiratory tract **(with nasopharyngeal involvement)** and kidney with necrotizing vasculitis.	Respiratory and sinus symptoms. Cavitary pulmonary lesions bleed and lead to **hemoptysis.**	Presence of **c-ANCA.** Segmental necrotizing glomerulonephritis.	High-dose corticosteroids, cytotoxic agents, or rituximab. Patients tend to have frequent relapses.
Microscopic polyangiitis	Small vessel vasculitis similar to GPA. **No granulomas.**	Similar to GPA but **no nasopharyngeal** involvement.	**p-ANCA.** Necrotizing glomerulonephritis.	Glucocorticoids, cyclophosphamide, or rituximab.
Eosinophilic granulomatosis with polyangiitis (Churg Strauss)	Small vessel vasculitis.	**Asthma,** sinusitis, skin nodules/purpura, peripheral neuropathy.	**p-ANCA.** ↑ IgE.	Glucocorticoids.
		ANTI-GBM DISEASE		
Goodpasture syndrome	Rapidly progressing glomerulonephritis with pulmonary hemorrhage; peak incidence is in men in their mid-20s.	**Hemoptysis,** dyspnea, possible respiratory failure. **No** upper respiratory tract involvement.	**Linear anti-GBM deposits** on immunofluorescence; iron deficiency anemia; hemosiderin-filled macrophages in sputum; pulmonary infiltrates on CXR.	**Plasma exchange therapy;** pulsed steroids. May progress to ESRD.
Alport syndrome	Hereditary glomerulonephritis; presents in boys 5–20 years of age.	Asymptomatic hematuria associated with **sensorineural deafness** and eye disorders.	GBM splitting on EM.	Progresses to renal failure. Anti-GBM nephritis may recur after transplant.

Diagnosis

- UA shows **proteinuria** (≥ 3.5 g/day) and lipiduria (Maltese crosses signifying lipids on microscopic urine examination). **Use spot protein-to-creatinine ratio** rather than 24-hour urine.
- Blood chemistry shows ↓ **albumin** (< 3 g/dL) and hyperlipidemia.
- Evaluation should include workup for 2° causes.
- Renal biopsy is used to definitively diagnose the underlying etiology.



A B

FIGURE 2.16-10. Findings in nephritic syndromes. (A) "Lumpy-bumpy" immunofluorescence found in postinfectious glomerulonephritis. **(B)** Linear immunofluorescence seen in Goodpasture syndrome. (Part A reproduced with permission from Oda T, Yoshizawa N, Yamakami K, et al. The role of nephritis-associated plasmin receptor (NAPLR) in glomerulonephritis associated with streptococcal infection, Biomed Biotechnol 2012;2012:417675. Part B reproduced with permission from Kasper D et al. Harrison's Principles of Internal Medicine, 19th ed. New York, NY: McGraw-Hill; 2015.)

Treatment

- Treat with **protein and salt restriction,** judicious diuretic therapy, and antihyperlipidemics.
- Immunosuppressant medications may be useful for certain etiologies.
- **ACEIs** ↓ proteinuria and diminish the progression of renal disease in patients with renal scarring (especially in diabetics).
- Vaccinate with 23-polyvalent pneumococcus vaccine (PPV23), as patients are at ↑ risk of Streptococcus pneumoniae infection.

Nephrolithiasis

Renal calculi. Stones are most commonly calcium oxalate, but many other types exist (see Table 2.16-6 and Figure 2.16-12). Risk factors include a ⊕ family history, **low fluid intake,** gout, medications (allopurinol, chemotherapy, loop diuretics), postcolectomy/postileostomy, specific enzyme deficiencies, type I RTA (due to alkaline urinary pH and associated hypocitruria), and hyperparathyroidism. Most common in older men.

KEY FACT

Which bacteria are associated with "staghorn calculi"? Urease-producing organisms such as Proteus.

History/Pe

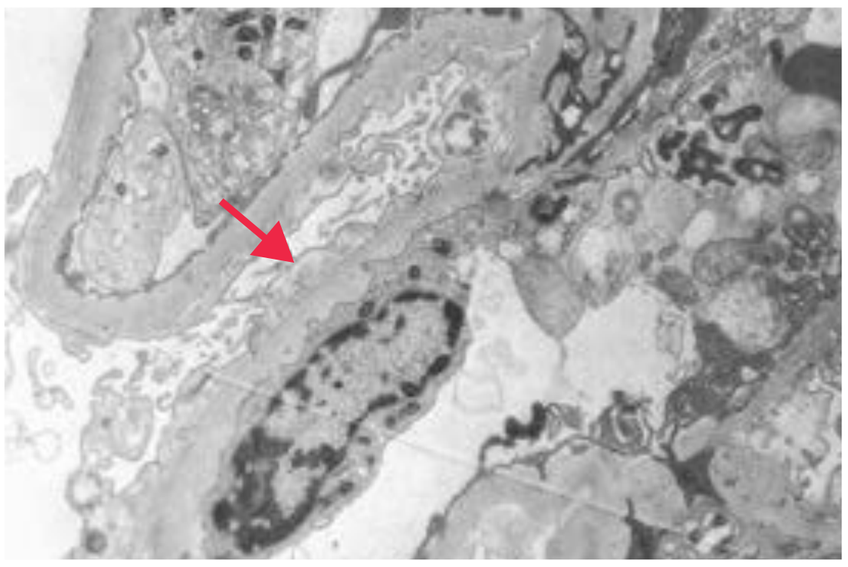
- Presents with **acute onset of severe, colicky flank pain** that may **radiate to the testes or vulva** and is associated with nausea and vomiting.
- Patients are unable to get comfortable and shift position frequently (as opposed to those with peritonitis, who lie still).

Diagnosis

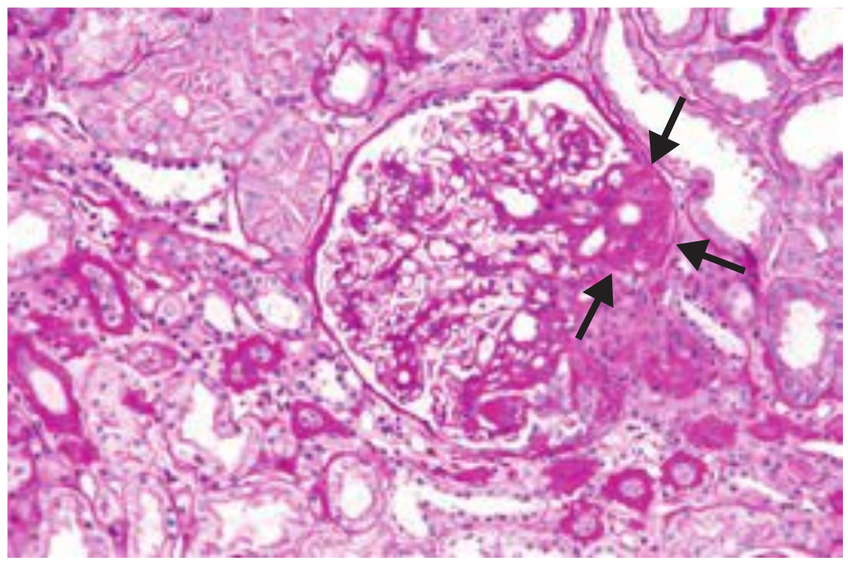
- UA may show gross or **microscopic hematuria** (85%) and an **altered urine pH.**
- **Noncontrast abdominal CT scan is the gold standard** for the diagnosis of kidney stones (see Figure 2.16-13). However, plain AXRs are still useful for following the progression/treatment of larger stones.
- **Ultrasonography is preferred for pregnant patients and children,** in whom radiation from CT should be avoided.

TABLE 2.16-5. Causes of Nephrotic Syndrome

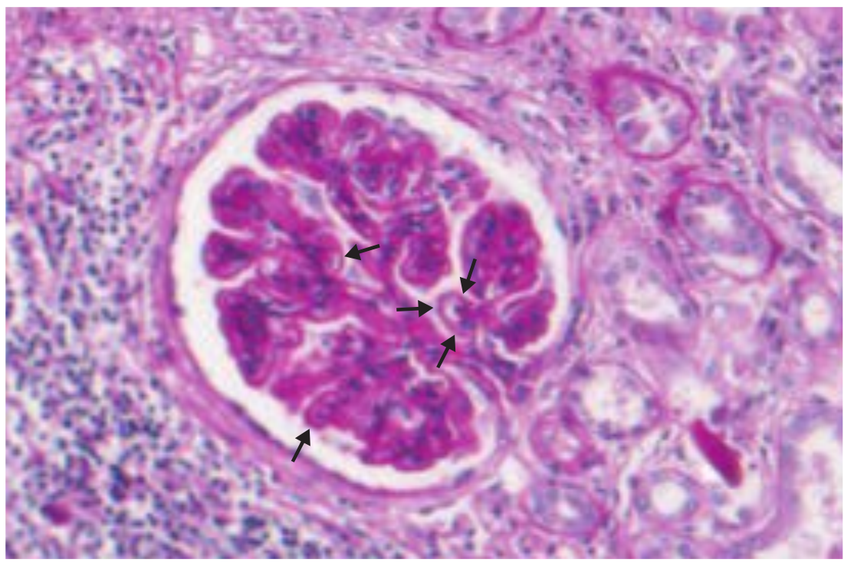
disorder	description	history/pe	labs/histology	treatment/prognosis
Minimal-change disease	The most common cause of nephrotic syndrome in **children.** Idiopathic etiology; 2° causes include NSAIDs and hematologic malignancies (eg, **Hodgkin disease**).	Tendency toward infections and thrombotic events. Sudden onset of edema.	Light microscopy appears **normal;** EM shows **fusion of epithelial foot processes** with lipid-laden renal cortices.	Steroids; excellent prognosis.
Focal segmental glomerulosclerosis	Idiopathic, **IV drug use (heroin), HIV,** obesity. The most common cause of nephrotic syndromes in adults overall.	The typical patient is a young **African American** man with uncontrolled hypertension.	Microscopic hematuria; biopsy shows sclerosis in capillary tufts.	Prednisone, cytotoxic therapy, ACEIs/ARBs to ↓ proteinuria.
Membranous nephropathy	Accounts for ~ 30% of nephrotic syndromes in adults.	Associated with **solid-tumor malignancies,** infections (HBV, malaria), autoimmune (SLE), drugs (NSAIDs, gold).	**"Spike-and-dome"** appearance due to granular deposits of IgG and C3 at the basement membrane.	Prednisone and cytotoxic therapy for severe disease.
Diabetic nephropathy	Has 2 characteristic forms: diffuse yalinization and nodular glomerulosclerosis **(Kimmelstiel-Wilson lesions).**	Patients generally have long-standing, poorly controlled DM with evidence of retinopathy or neuropathy.	Thickened GBM; ↑ **mesangial matrix.**	Tight control of blood sugar; ACEIs or ARBs.
Lupus nephritis	Classified as WHO types I–VI. Both nephrotic and nephritic. The severity of renal disease often determines overall prognosis.	Proteinuria or RBCs on UA may be found during evaluation of SLE patients.	Mesangial proliferation; subendothelial and/or subepithelial immune complex deposition.	Prednisone and cytotoxic therapy may slow disease progression.
Renal amyloidosis	1° (plasma cell dyscrasia) and 2° (infectious or inflamm tory) are the most common.	Patients may have multiple myeloma or a chronic inflamm tory disease (eg, **rheumatoid arthritis,** TB).	Nodular glomerulosclerosis; EM reveals amyloid fib ils; **apple-green** birefringence with Congo red stain.	Prednisone and melphalan. Bone marrow transplantation may be used for multiple myeloma.
MeMbranoproliFerative nephropathy				
Type I	Nephritic/nephrotic syndrome.	Associated with HBV, HCV, cryoglobulinemia, SLE, and subacute bacterial endocarditis.	**"Tram-track,"** double-layered basement membrane. Subendothelial and mesangial deposits. Low serum C3.	Corticosteroids and cytotoxic agents may help.
Type II/III	Nephritic/nephrotic.	Often idiopathic.	Intramembranous dense deposits. Occurs by way of C3 nephritic factor.	Same.



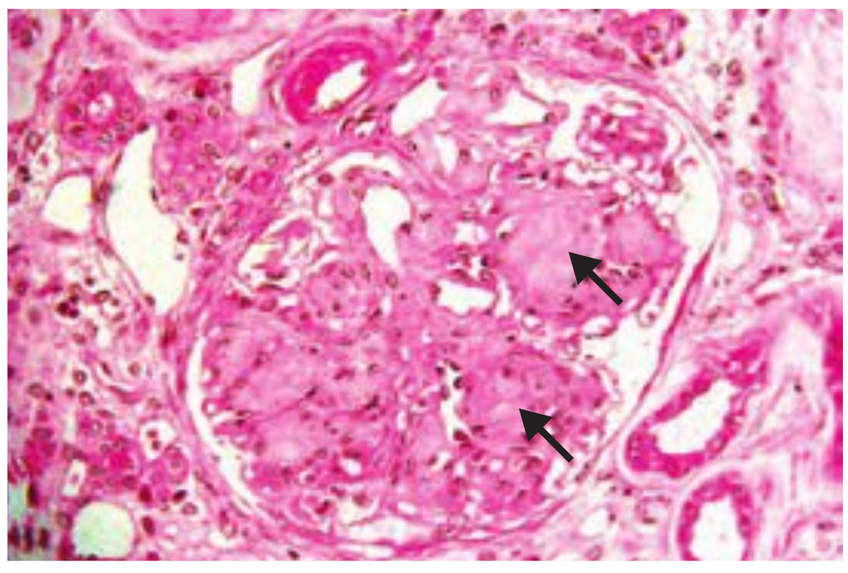
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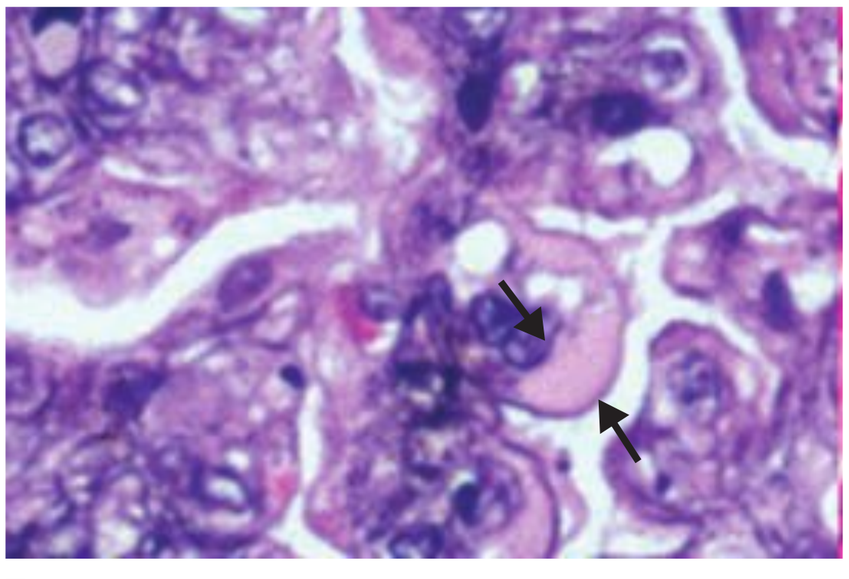
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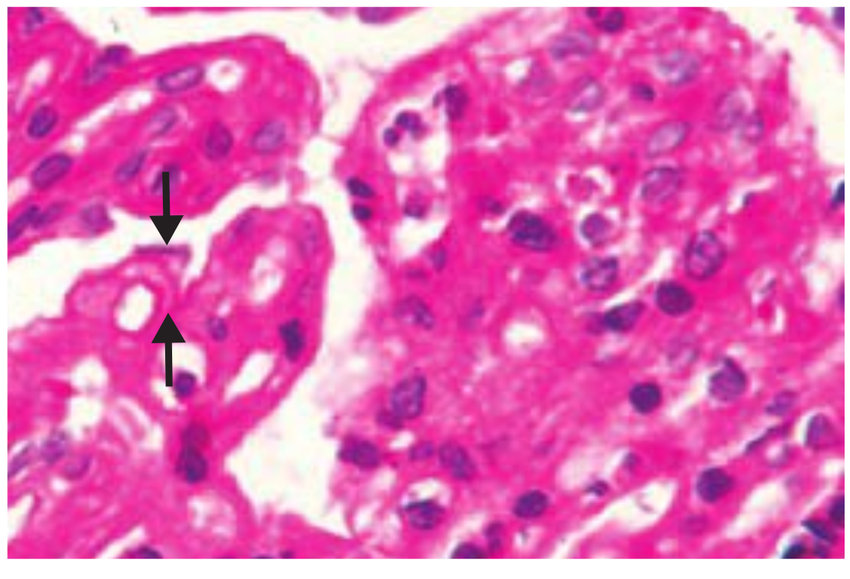
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E



F

FIGURE 2.16-11. Findings in nephrotic syndromes. (A) Minimal change disease findings on electron microscopy indicating effacement of foot processes (arrows). **(B)** Focal segmental glomerulosclerosis (arrows). **(C)** Membranous nephropathy with capillary and GBM thickening (arrows). **(D)** Kimmelstiel-Wilson lesions in diabetic nephropathy. **(E, F)** "Tram-track" appearance due to splitting of the basement membrane seen in membranoproliferative nephropathy. (Part A reproduced with permission from Le T et al. First Aid for the USMLE Step 1 2015. New York, NY: McGraw-Hill; 2015. Part B modified with permission from Nephron. Parts C, E, F reproduced with permission from USMLE-Rx.com. Part D used with permission from Doc Mari.)

- KUB (kidney/ureter/bladder) radiography identifies radiopaque stones but will often miss stones that are radiolucent.
- IVP is rarely used.

Treatment

- **Hydration and analgesia** are the initial treatment.
- Kidney stones < 5 mm in diameter can pass through the urethra; stones 0.5–3 cm in diameter can be treated with **extracorporeal shockwave lithotripsy (ESWL),** percutaneous nephrolithotomy, or retrograde ureteroscopy.

TABLE 2.16-6. Types of Nephrolithiasis

Type	Frequency	Etiology and Characteristics	Urinary pH	Treatment
Calcium oxalate/ calcium phosphate	83%	The most common causes are **idiopathic hypercalciuria** and 1° hyperparathyroidism. Can also see in fat malabsorption (↑ oxalate absorption). Alkaline urine. Radiopaque.	↑ pH (calcium phosphate). ↓ pH (calcium oxalate).	Hydration, dietary sodium and protein restriction, thiazide diuretics. Do not ↓ calcium intake (can lead to hyperoxaluria and an ↑ risk of osteoporosis).
Struvite ($Mg\text{-}NH_4\text{-}PO_4$) or "triple phosphate"	9%	Associated with urease-producing organisms (eg, Proteus). Form **staghorn calculi.** Alkaline urine. Radiopaque.	↑ pH	Hydration; treat UTI if present; surgical removal of staghorn stone.
Uric acid	7%	Associated with gout, xanthine oxidase deficien y, and high purine turnover states (eg, chemotherapy). Acidic urine (pH < 5.5). **Radiolucent** on plain film, but detectable with CT.	↓ pH	Hydration; alkalinize urine with **citrate,** which is converted to HCO_3^- in the liver; dietary purine restriction and allopurinol.
Cystine	1%	Due to a defect in renal transport of certain amino acids (**COLA**—cystine, ornithine, lysine, and arginine). **Hexagonal crystals.** ⊕ **urinary cyanide nitroprusside test.** Radiopaque.	↓ pH	Hydration, dietary sodium restriction, alkalinization of urine, penicillamine.

- Can also consider medical treatment with α-blockers or calcium channel blockers to facilitate stone passage.
- Dietary changes to prevent calcium stones include ↑ fluid intake (most important), ↑ **calcium intake,** ↓ dietary protein/oxalate intake, and ↓ sodium intake.

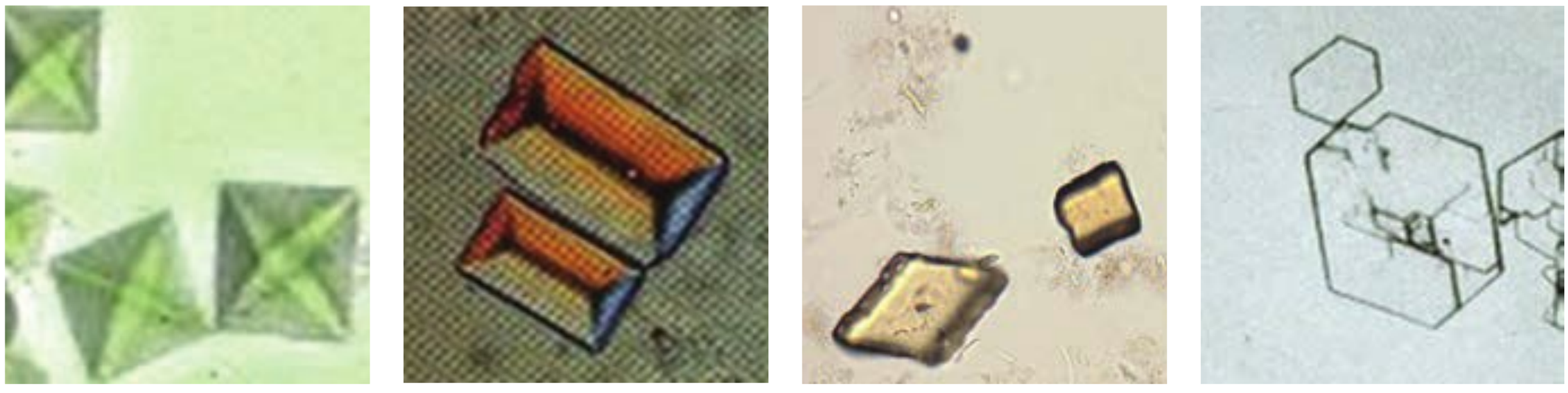


FIGURE 2.16-12. Crystals found in nephrolithiasis. (A) Envelope-shaped in calcium oxalate stones. **(B)** Coffin lid-shaped in ammonium magnesium phosphate stone. **(C)** Rhomboid in uric acid stones. **(D)** Hexagonal in cystine stones. (Reproduced with permission from Le Tet al. First Aid for the USMLE Step 1 2015. New York, NY: McGraw-Hill; 2015.)

Polycystic Kidney Disease

Characterized by the presence of progressive cystic dilation of the renal tubules, as well as by cysts in the spleen, liver, and pancreas. The two major forms are as follows:

- **Autosomal dominant (ADPKD):**
  - Most common.
  - Usually asymptomatic until patients are > 30 years of age.
  - One-half of ADPKD patients will have ESRD requiring dialysis by age 60.
  - Associated with an ↑ risk of cerebral aneurysm, especially in patients with a ⊕ family history.
- **Autosomal recessive (ARPKD):** Less common but more severe. Presents in infants and young children with renal failure, liver fibrosis, and portal hypertension; can lead to death in the first few years of life.

History/Pe

- **Pain and hematuria** are the most common presenting symptoms. Sharp, localized pain may result from cyst rupture, infection, or passage of renal calculi.
- Additional findings include **hypertension, hepatic cysts, cerebral berry aneurysms,** diverticulosis, and mitral valve prolapse.
- Patients may have large, palpable kidneys on abdominal exam.

Diagnosis

Based on ultrasonography (most common) or CT scan (see Figure 2.16-14). Multiple bilateral cysts will be present throughout the renal parenchyma, and renal enlargement will be visualized. Genetic testing by DNA linkage analysis for ADPKD1 and ADPKD2 is available.

Treatment

- **Prevent complications and ↓ the rate of progression to ESRD.** Early management of UTIs is critical to prevent renal cyst infection. BP control (ACEIs, ARBs) is necessary to ↓ hypertension-induced renal damage.
- Dialysis and renal transplantation are used to manage patients with ESRD.

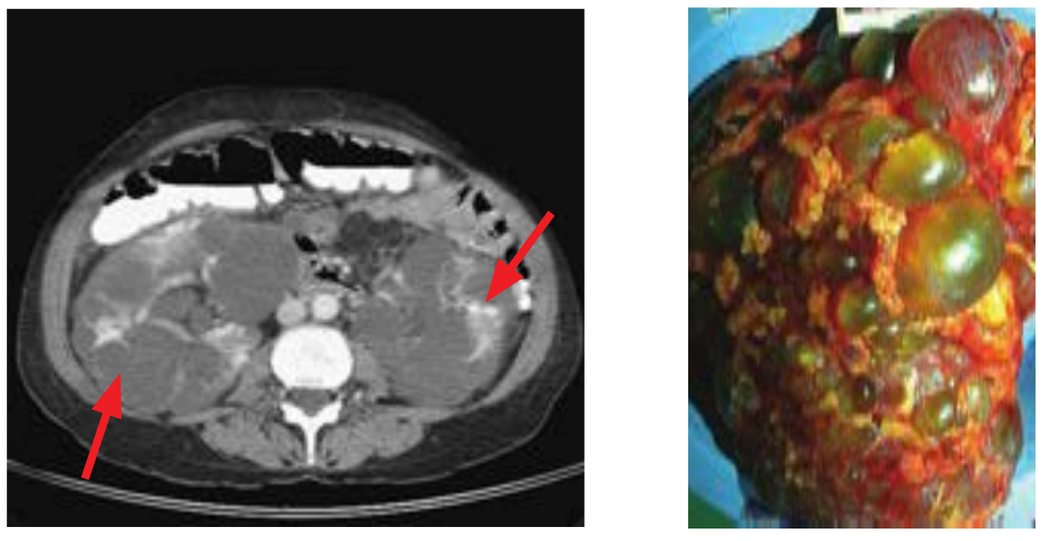


FIGURE 2.16-13. Nephrolithiasis. CT scan shows a dense 1-cm calcification (arrow) in the left ureter, consistent with nephrolithiasis. (Reproduced with permission from Tintinalli JE et al. Tintinalli's Emergency Medicine: A Comprehensive Study Guide, 7th ed. New York, NY: McGraw-Hill; 2011.)

KEY FACT

If a patient with known ADPKD develops a sudden-onset, severe headache, you must rule out subarachnoid hemorrhage from a ruptured berry aneurysm!

A B

FIGURE 2.16-14. Autosomal dominant polycystic kidney disease. (A) Contrast-enhanced CT scan demonstrates bilaterally enlarged kidneys that have been almost entirely replaced by cysts (arrows). **(B)** Gross specimen of a right kidney from a patient with ADPKD who underwent renal transplantation. (Image A reproduced with permission from Fauci AS et al. Harrison's Principles of Internal Medicine, 17th ed. New York, NY: McGraw-Hill; 2008. Image B reproduced with permission from USMLE-Rx.com.)

Hydronephrosis

KEY FACT

Left untreated, hydronephrosis resulting from urinary obstruction leads to hypertension, acute or chronic renal failure, or sepsis, and has a very poor prognosis.

Dilation of renal calyces. Usually occurs 2° to obstruction of the urinary tract. In pediatric patients, the obstruction is often at the ureteropelvic junction. In adults, it may be due to BPH, neurogenic bladder (diabetics/spinal cord injuries), tumors, aortic aneurysms, or renal calculi. Can also be caused by high-output urinary flow and vesicoureteral reflux.

History/Pe

May be asymptomatic, or may present with flank/back pain, ↓ urine output, abdominal pain, and UTIs.

Diagnosis

- **Ultrasonography** or CT scan to detect dilation of the renal calyces and/or ureter (see Figure 2.16-15).
- ↑ BUN and creatinine provide evidence of 2° renal failure.

Treatment

- Surgically correct any anatomic obstruction; use laser or sound wave lithotripsy if calculi are causing obstruction.
- Ureteral stent placement across the obstructed area of the urinary tract and/or percutaneous nephrostomy tube placement to relieve pressure may be appropriate if the urinary outflow tract is not sufficiently cleared of obstruction. Foley or suprapubic catheters may be required for lower urinary tract obstruction (eg, **BPH**).

Scrotal Swelling

- **Painless** etiologies → hydrocele (remnant of processus vaginalis), varicocele (dilatation of pampiniform plexus).
- **Painful** etiologies → epididymitis (STDs, prostatitis), testicular torsion (twisting of the spermatic cord).

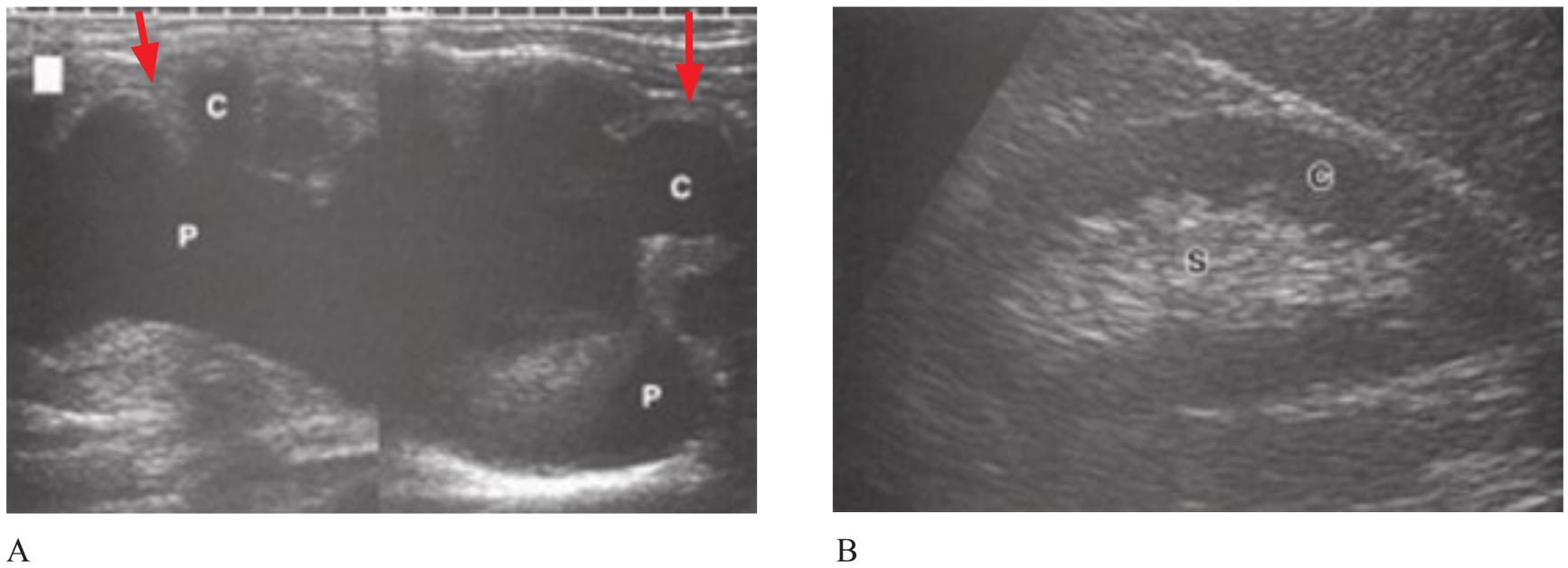


FIGURE 2.16-15. Hydronephrosis. (A) Ultrasound of a renal transplant shows severe hydronephrosis, with dilation of the renal pelvis (P) and the renal calyces (C). The overlying renal cortex is severely thinned (arrows). **(B)** Normal renal ultrasound for comparison. C = cortex; S = sinus fat. (Reproduced with permission from Tanagho EA, McAninch JW. Smith's General Urology, 17th ed. New York, NY: McGraw-Hill; 2008.)

History/Pe

Physical exam reveals "bag of worms" in varicocele, more often in **left testicle** than right. ⊕ **Prehn sign** (↓ pain with scrotal elevation) in **epididymitis,** ⊖ **Prehn sign in torsion.**

Diagnosis

Hydrocele will **transilluminate on ultrasonogram,** varicocele will **not.** Doppler ultrasonography shows normal to ↑ blood flow to testes in epididymitis, ↓ blood flow in torsion (see Figure 2.16-16). UA and culture will often show Neisseria gonorrhoeae, Escherichia coli, or Chlamydia in epididymitis.

Treatment

- **Hydrocele:** None needed. Will typically resolve. Does have an ↑ risk of indirect inguinal hernia.
- **Varicocele: May need surgery if large or symptomatic.**
- **Epididymitis:** Antibiotics (tetracycline, fluoroquinolones); NSAIDs; scrotal support for pain.
- **Testicular torsion:** Immediate surgery (under 6 hours) to salvage testis. Attempt manual detorsion only if surgery is unavailable or if it will not delay surgery. Orchiopexy of **both** testes to prevent future torsion.

Erectile Dysfunction

Found in 10–25% of middle-aged and elderly men. Classified as failure to initiate (eg, psychological, endocrinologic, neurologic), failure to fill (eg, arteriogenic), or failure to store (eg, veno-occlusive dysfunction). Risk factors include **DM, atherosclerosis, medications** (eg, **β-blockers,** SSRIs, TCAs, diuretics), hypertension, heart disease, surgery or radiation for prostate cancer, and spinal cord injury.

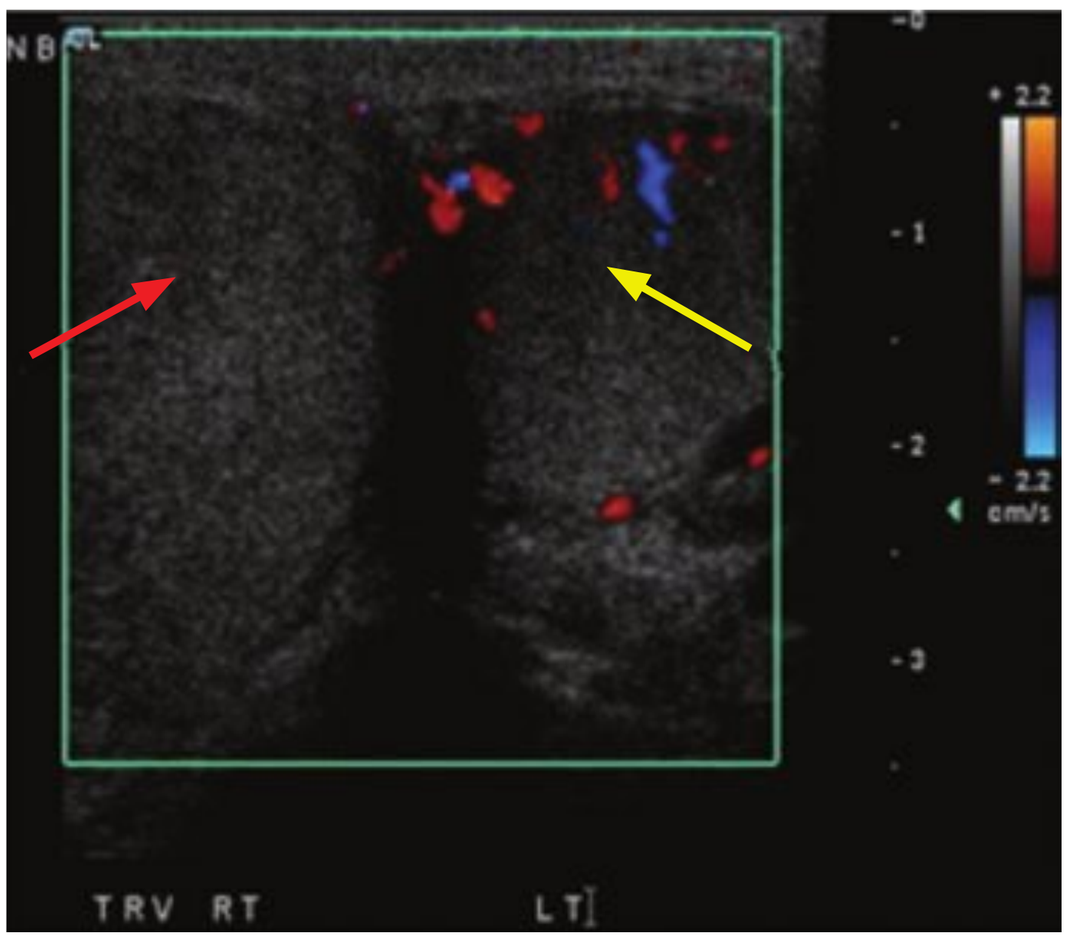


FIGURE 2.16-16. Testicular torsion. Transverse Doppler image through the scrotum demonstrates asymmetric swelling and decreased blood flow to the right testis (red arrow) compared to the left testis (yellow arrow) in this patient with acute right testicular pain. (Reproduced with permission from USMLE-Rx.com.)

Q 1

A 26-year-old woman with a history of depression presents to the ED with altered mental status, tinnitus, nausea, and vomiting. An ABG shows a pH of 7.4, $Paco_2$ of 22, and a HCO_3^- of 13. What is the most likely diagnosis, and what is her acid-base disorder?

Q 2

A 17-year-old boy with a history of asthma presented to the ED with severe shortness of breath. His arterial pH has gone from 7.49 to 7.38 since the time of admission. What is the next best step in management?

Q 3

A 37-year-old homeless man was found unconscious on a park bench. Upon waking, he complains of muscle soreness and dark urine. His urine dipstick is ⊕ for blood. What is the likely cause of this finding, and what is the best next step?

KEY FACT

"**P**oint and **S**hoot": The **P**arasympathetic nervous system mediates erection; the **S**ympathetic nervous system mediates ejaculation.

KEY FACT

Nitrates and phosphodiesterase 5 inhibitors (Viagra) are a dangerous combination → the combined effect of ↓ BP can lead to myocardial ischemia.

1 A

Aspirin overdose. Though her pH is normal, she has a mixed **metabolic acidosis and respiratory alkalosis.** Her bicarbonate is low, indicating a metabolic acidosis. Winter's formula predicts that her $Paco_2$ under normal compensation should be 29 ($Paco_2 = 1.5 (HCO_3^-) + 8$). Her $Paco_2$ is lower than this at 22, which indicates a concurrent **respiratory alkalosis.**

2 A

This is a sign of respiratory muscle fatigue and may require urgent intubation.

3 A

This patient probably has rhabdomyolysis, and the urine dipstick is detecting myoglobin. He should be managed with saline hydration, mannitol, bicarbonate, and an ECG to rule out life-threatening hyperkalemia.

History/Pe

- Ask about risk factors (diabetes, peripheral vascular disease), **medication use,** recent life changes, and psychological stressors.
- The distinction between psychological and organic ED is based on the presence of **nocturnal or early-morning erections** (if present, it is nonorganic) and on **situation dependence** (ie, occurring with only one partner).
- Evaluate for **neurologic dysfunction** (eg, anal tone, lower extremity sensation) and for **hypogonadism** (eg, small testes, loss of 2° sexual characteristics).

Diagnosis

- **Clinical diagnosis.**
- **Other workup: Testosterone** and **gonadotropin** levels may be abnormal. Elevated **prolactin** can result in ↓ androgen activity.

Treatment

- Patients with psychological ED may benefit from psychotherapy involving discussion and exercises with the partner.
- Oral **sildenafil (Viagra), vardenafil (Levitra), and tadalafil (Cialis)** are phosphodiesterase-5 (PDE5) inhibitors that result in prolonged action of cGMP-mediated smooth muscle relaxation and ↑ blood flow in the corpora cavernosa.
- **Testosterone** is a useful therapy for patients with hypogonadism of testicular or pituitary origin; it is discouraged for patients with normal testosterone levels.
- Vacuum pumps, intracavernosal prostaglandin injections, and surgical implantation of semirigid or inflatable penile prostheses are alternatives for patients for whom PDE5 therapy fails.

Benign Prostatic Hyperplasia

Enlargement of the prostate that is a normal part of the aging process and is seen in **> 80% of men by age 80.** Most commonly presents in men **> 50 years of age.** BPH can coexist with prostate cancer, but BPH does **not** cause prostate cancer.

History/Pe

- **Obstructive symptoms:** Hesitancy, weak stream, intermittent stream, incomplete emptying, urinary retention, bladder fullness.
- **Irritative symptoms:** Nocturia, daytime frequency, urge incontinence, opening hematuria.
- On digital rectal examination, the prostate is uniformly enlarged with a rubbery texture. If the prostate is hard or has irregular lesions, cancer should be suspected.

Diagnosis

- Conduct a **DRE** to screen for masses; if findings are suspicious, evaluate for prostate cancer.
- Obtain a **UA and urine culture** to rule out infection and hematuria.
- Initial PSA testing recommended, though often elevated in BPH. Further workup needed if elevated PSA correlates with other findings suspicious for prostate cancer.
- Consider **creatinine levels** to rule out obstructive uropathy and renal insufficiency.

Treatment

- **Medical therapy** includes α-blockers (eg, tamsulosin, terazosin), which relax smooth muscle in the prostate and bladder neck, as well as 5α-reductase inhibitors (eg, finasteride), which inhibit the production of dihydrotestosterone.
- Transurethral resection of the prostate (TURP) or open prostatectomy is appropriate for patients with moderate to severe symptoms/complications (including renal insufficiency, recurrent UTIs, bladder stones).

KEY FACT

BPH most commonly occurs in the central (periurethral) zone of the prostate and may not be detected on DRE.

Prostate Cancer

The **most common cancer in men** and the **second leading cause of cancer death** in men (after lung cancer). Risk factors include advanced age and a ⊕ family history.

KEY FACT

Leading causes of cancer death in men:
1. Lung cancer
2. Prostate cancer
3. Colorectal cancer
4. Pancreatic cancer

History/Pe

- Usually **asymptomatic,** but may present with **obstructive urinary symptoms** as well as with lymphedema due to obstructing metastases, constitutional symptoms, and **back pain due to bone metastases.**
- DRE may reveal a **palpable nodule** or an area of induration (see Figure 2.16-17). Early carcinoma is usually not detectable on examination.
- A tender prostate suggests prostatitis.

Diagnosis

- Suggested by clinical findings and/or a markedly ↑ **PSA** (> 4 ng/mL).
- Definitive diagnosis is made with **ultrasound-guided transrectal** biopsy.
- Tumors are graded by the **Gleason histologic system,** which sums the scores (from 1 to 5) of the two most dysplastic samples (10 is the highest grade).
- Look for metastases with CT of the abdomen/pelvis and **bone scan** (metastatic lesions show an **osteoblastic** or ↑ bone density).

Treatment

- **Watchful waiting** may be the best approach for elderly patients with low-grade tumors, as many cases of prostate cancer are slow to progress.
- **Radical prostatectomy** is associated with an ↑ risk of incontinence and/

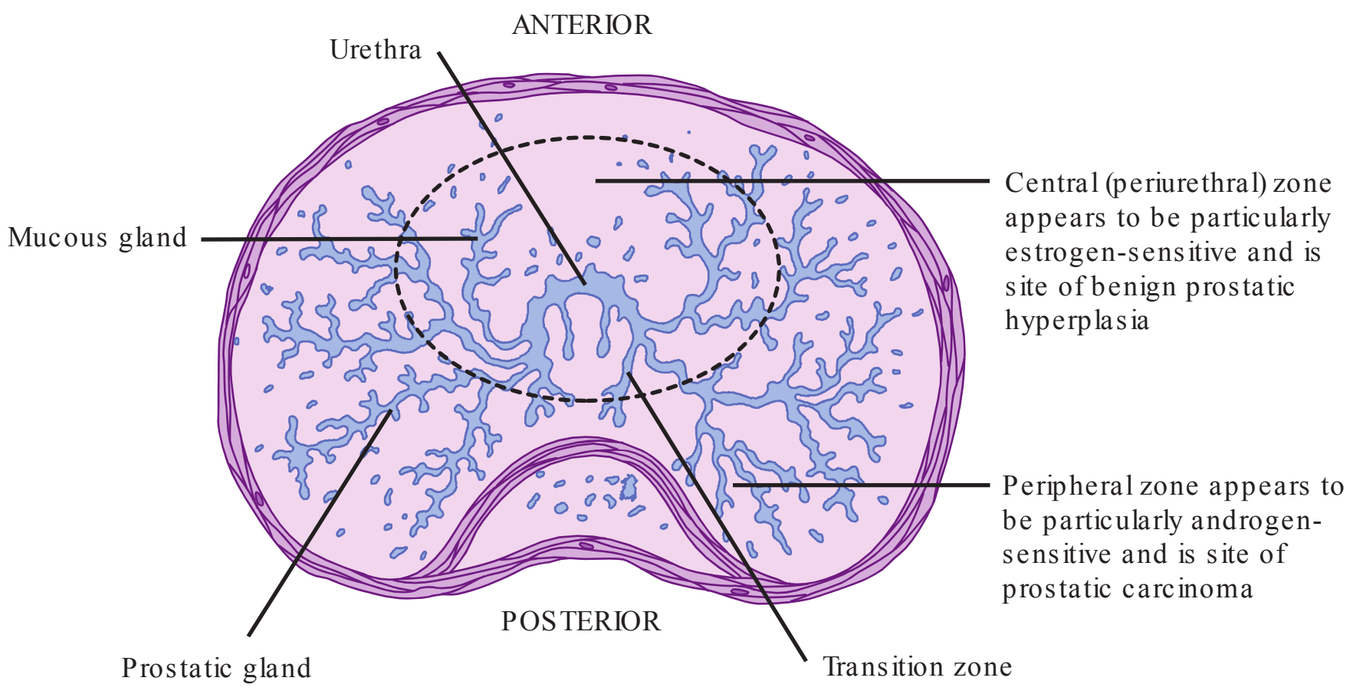


FIGURE 2.16-17. Structure of the prostate. (Adapted with permission from Chandrasoma P, Taylor CE. Concise Pathology, 3rd ed. Stamford, CT: Appleton & Lange; 1998.)

Q 1

A 68-year-old woman with a history of hepatitis and CKD presents with RUQ abdominal pain. A CT scan identifies liver cirrhosis. Two days later, her creatinine levels have doubled. What is the likely cause, and what could have prevented this outcome?

Q 2

A 19-year-old man with a history of recurrent kidney stones presents with acute left flank pain. His father also has a history of kidney stones. A urinary cyanide nitroprusside test is ⊕. A CT scan confirms nephrolithiasis. What is the most likely diagnosis?

KEY FACT

An ↑ PSA can be due to BPH, prostatitis/UTI, prostatic trauma, or carcinoma.

or erectile dysfunction. **Radiation therapy** (eg, brachytherapy or external beam) is associated with an ↑ risk of radiation proctitis and GI symptoms.

- **PSA,** while controversial as a screening test, is used to follow patients post-treatment to evaluate for disease recurrence.
- Treat metastatic disease with **androgen ablation** (eg, gonadotropin-releasing hormone agonists, orchiectomy, flutamide) and chemotherapy.

Prevention

Screening guidelines remain controversial. Men should discuss the pros and cons of annual DRE and/or PSA testing starting at age 50**.** Screening should begin earlier in African American men and in those with a first-degree relative with prostate cancer.

Bladder Cancer

MNEMONIC

Differential for hematuria—

I PEE RBCS

Infection (UTI)
Polycystic kidney disease
Exercise
External trauma
Renal glomerular disease
Benign prostatic hyperplasia
Cancer
Stones

The second most common urologic cancer and the most frequent malignant tumor of the urinary tract; usually a **transitional cell carcinoma (**Figure 2.16-18**).** Most prevalent in men during the sixth and seventh decades. Risk factors include **smoking,** diets rich in meat and fat, schistosomiasis, chronic treatment with cyclophosphamide, and occupational exposure to **aniline dye.**

History/Pe

- **Gross hematuria** is the most common presenting symptom.
- Other urinary symptoms, such as frequency, urgency, and dysuria, can also be seen, but most patients are asymptomatic in the early stages of disease.

Diagnosis

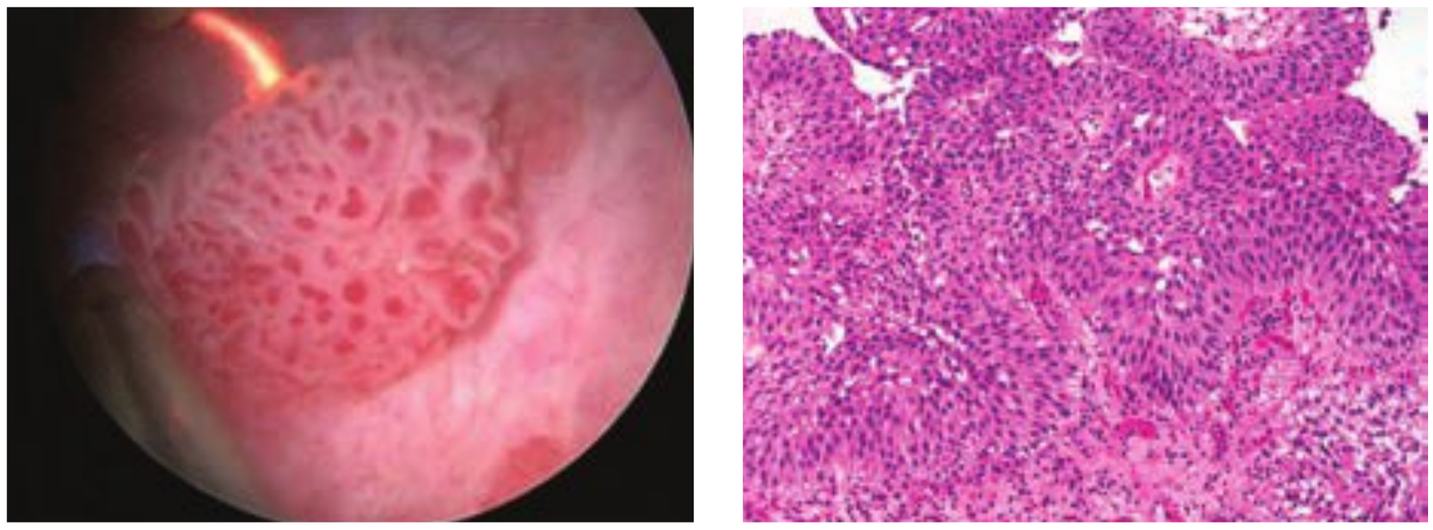
- **Cystoscopy with biopsy is diagnostic** and is recommended in the evaluation of older adults to rule out malignancy.
- **UA** often shows hematuria (macro- or microscopic).
- **Cytology** may show dysplastic cells.
- **MRI, CT,** and bone scan are important tools with which to define invasion and metastases.

1 **A**

The patient probably has contrast-induced nephropathy and would have benefted from saline hydration before and during the CT scan.

2 **A**

Cystinuria. Decreased cystine reabsorption due to a defect in proximal tubular transport. You would also probably see hexagonal crystals on UA.



A B

FIGURE 2.16-18. Transitional cell carcinoma of the bladder. (A) Cystoscopic image of bladder wall mass. **(B)** Papillary growth lined by transitional epithelium with mild nuclear atypia and pleomorphism. (Part A adapted with permission from Geavlete B, Stanescu F, Moldoveanu C, et al. NBI cystoscopy and bipolar electrosurgery in NMIBC management—an overview of daily practice. J Med Life 2013 Jun 15;6(2):140–145. Part B reproduced with permission from Le T et al. First Aid for the USMLE Step 1 2015. New York, NY: McGraw-Hill; 2015.)

Treatment

Treatment depends on the extent of spread beyond the bladder mucosa.

- **Carcinoma in situ:** Intravesicular chemotherapy.
- **Superficial cancers:** Complete transurethral resection or intravesicular chemotherapy with mitomycin-C or BCG (the TB vaccine).
- **Large, high-grade recurrent lesions:** Intravesicular chemotherapy.
- **Invasive cancers without metastases:** Radical cystectomy or radiation therapy for patients who are deemed poor candidates for radical cystectomy as well as for those with unresectable local disease.
- **Invasive cancers with distant metastases:** Chemotherapy alone.

KEY FACT

The next best step for diagnosis in a patient with **unexplained hematuria** is cystoscopy to evaluate for **bladder cancer.**

Renal Cell Carcinoma

An adenocarcinoma from tubular epithelial cells (~ 80–90% of all malignant tumors of the kidney). Tumors can spread along the renal vein to the IVC and can metastasize to lung and bone. Risk factors include **male gender, smoking, obesity, acquired cystic kidney disease in ESRD,** and von Hippel–Lindau disease.

History/Pe

- Presenting signs include **hematuria, flank pain,** and a **palpable flank mass.** Metastatic disease can present with weight loss and malaise.
- Many patients have **fever** or other constitutional symptoms. Left-sided varicocele can be seen in men (due to tumor blockage of the left gonadal vein, which empties into the left renal vein; the right gonadal vein empties directly into the IVC).
- **Anemia is common at presentation,** but **polycythemia** due to ↑ erythropoietin production can be seen in 5–10% of patients.

KEY FACT

The classic triad of renal cell carcinoma is hematuria, flank pain, and a palpable flank mass, but only 5–10% present with all three components of the triad.

KEY FACT

In a middle-aged smoker with a left-sided varicocele, think renal cell carcinoma!

Diagnosis

Diagnosed via CT (see Figure 2.16-19) to characterize the renal mass and stage for lymph nodes/metastases. Ultrasonography rarely used. Diagnosis then confirmed by histology on nephrectomy specimen.

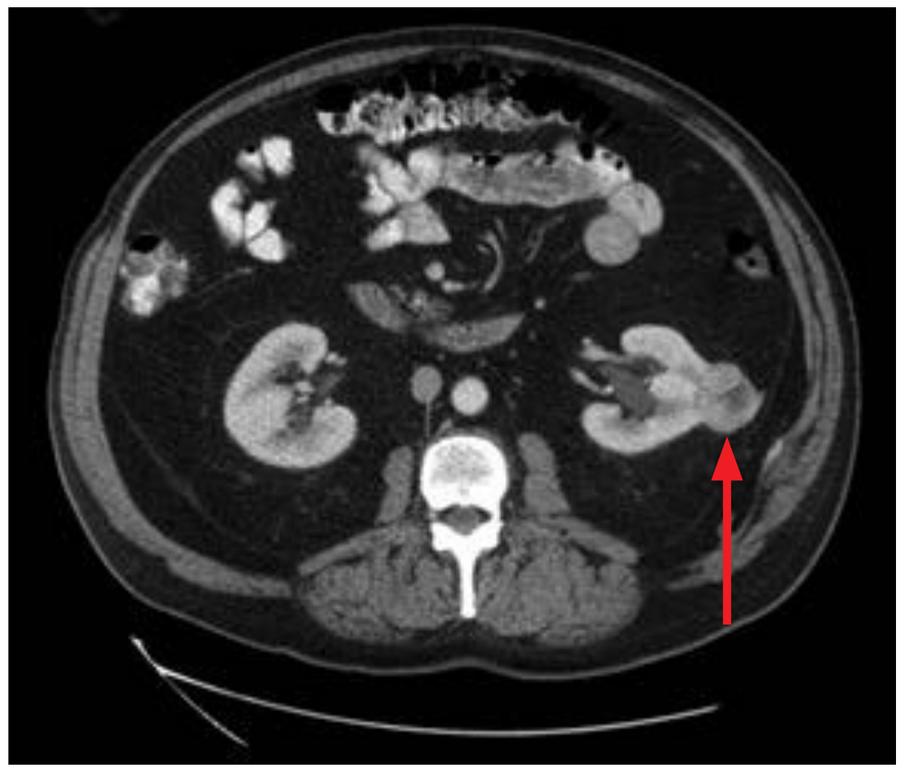


FIGURE 2.16-19. Renal cell carcinoma. A contrast-enhanced CT through the abdomen demonstrates an enhancing exophytic mass (arrow) in the left kidney that proved on pathology to be renal cell carcinoma. (Reproduced with permission from Doherty GM. Current Diagnosis & Treatment: Surgery, 13th ed. New York, NY: McGraw-Hill; 2010.)

Treatment

- **Surgical resection** may be curative in localized disease. Metastasectomy may improve survival in metastatic disease.
- Response rates from radiation or chemotherapy are only 15–30%. Newer tyrosine kinase inhibitors (sorafenib, sunitinib), which ↓ tumor angiogenesis and cell proliferation, have shown promising results and have recently been approved by the FDA for the treatment of renal cell carcinoma.

Testicular Cancer

A heterogeneous group of neoplasms. Some 95% of testicular tumors derive from **germ cells,** and **virtually all are malignant. Cryptorchidism** is associated with an ↑ risk of neoplasia in both testes. **Klinefelter syndrome** is also a risk factor. Testicular cancer is the most common malignancy in men 15–34 years of age.

History/Pe

- Patients most often present with **painless enlargement of the testes.**
- Most testicular cancers occur between ages 15 and 30, but seminomas have a peak incidence between 40 and 50 years of age.

KEY FACT

β-hCG in men = choriocarcinoma.

Diagnosis

- **Testicular** ultrasonography.
- **CXR** and abdominal/pelvic CT to evaluate for metastasis.
- **Tumor markers** are useful for diagnosis and in monitoring treatment response. See Table 2.16-7.

Treatment

- Radical orchiectomy.
- Seminomas are **exquisitely radiosensitive** and also respond to chemotherapy.
- Platinum-based chemotherapy is used for nonseminomatous germ cell tumors.

TABLE 2.16-7. Tumor Markers in Testicular Cancer

Type	Tumor Marker
Germ cell tumors (95% of all testicular tumors)	
Seminoma (most common testicular tumor)	↑ placental ALP
Yolk sac (endodermal sinus tumor)	↑ AFP
Choriocarcinoma	↑ β-hCG
Teratoma	AFP and/or β-hCG
Non-germ cell tumors (5% of all testicular tumors)	
Leydig cell	↑ testosterone and estrogen
Sertoli cell	None
Testicular lymphoma	None. Arises from a metastasis to testes

HIGH-YIELD FACTS IN

SELECTED TOPICS IN EMERGENCY MEDICINE

Trauma Management 494
- 1° Survey 494
- 2° Survey 494

Penetrating Trauma 497
- Neck 497
- Chest 497
- Abdomen 498
- Musculoskeletal 498

Blunt and Deceleration Trauma 498
- Head 498
- Chest 499
- Abdomen/Pelvis 501

Cardiac Life Support Basics 502

Acute Abdomen 502

Acute Appendicitis 504

Burns 506

Postoperative Fever 507

Shock 507

Thermal Dysregulation 508
- Hypothermia 508
- Hyperthermia 509

Bites and Stings 509

Toxicology 509
- Carbon Monoxide Poisoning 509
- Common drug Interactions/Reactions 511
- drug overdose 511
- Major drug Side Effects 511
- Management of drug Withdrawal 515
- Recognition of drug Intoxication 516

Vitamin Deficiencies 516

MNEMONIC

1° survey of a trauma patient—

ABCDE

Airway
Breathing
Circulation
Disability
Exposure

KEY FACT

Suspect thermal or inhalational injury to the airway in patients with singed nasal hairs, facial burns, hoarseness, wheezing, soot in the posterior oropharynx, or carbonaceous sputum.

KEY FACT

Remember the rhyme, "GCS < 8 = intubate!"

KEY FACT

To remember the GCS, think **EYES = 4 letters, VOICE = 5 letters, ARM + LEG = 6 letters:** 4 points can be assigned for eye response, 5 points for verbal response, and 6 points for motor response.

KEY FACT

Immediately evaluate trauma patients for open pneumothorax, tension pneumothorax (see Figure 2.17-2), flail chest, massive hemothorax, cardiac tamponade, and airway obstruction.

Trauma Management

The order of acute management of a trauma patient can be remembered with the mnemonic **ABCDE. Establishing and maintaining airway patency takes precedence over all other treatment.** Ensure sufficient respiratory support and adequate circulation for end-organ function. Table 2.17-1 describes disability assessment with the Glasgow Coma Scale.

1° SURVEY

Figure 2.17-1 illustrates the 1° issues to be surveyed on intake of a trauma patient.

2° SURVEY

- After the patient's ABCDEs are managed, conduct a full head-to-toe examination.
- For hemodynamically unstable patients, or those with a history of blunt trauma to the abdomen or chest, do a focused abdominal sonography for trauma **(FAST)** scan (Figure 2.17-3). Hemoperitoneum requires immediate surgical consultation for operative management; pericardial effusion warrants immediate pericardiocentesis to prevent cardiac tamponade (see Figure 2.17-4).
- After urethral injury has been ruled out, place a Foley catheter to monitor urine output in hemodynamically unstable patients receiving fluids, or those undergoing surgery.
- Order radiology studies on the basis of the patient assessment:
  - CXR for thoracic trauma.
  - Head CT (clinical decision guidelines assess factors such as age, altered mental status, suspected skull fracture, and mechanism of injury).
  - C-spine CT is needed for all patients with neck pain or tenderness, neurologic findings, or depressed mental status.
- Pertinent labs should address mechanism of injury, intoxication or overdose, and medical history.

TABLE 2.17-1. Glasgow Coma Scale Scoring

Score	Eye Opening Response (4)	Verbal Response (5)	Motor Response (6)
6			Follows commands
5		Oriented	Localizes pain
4	Spontaneous	Confused speech	Withdraws to pain
3	Opens to command	Inappropriate words	Flexion
2	Opens to pain	Incomprehensible	Extension
1	None	None	None

Airway
- Assess patient's ability to speak.
- Look for airway obstruction.
- Administer oxygen.
  Intubate patients with compromised airway (jaw thrust if necessary to protect C-spine). *May require surgical airway (cricothyroidotomy) for difficult intubations secondary to trauma/obstruction.

Breathing
- Auscultate breath sounds.
- If tension pneumothorax is suspected, perform needle decompression.
- Obtain CXR to rule out trauma.
- If pneumothorax or hemothorax suspected, place chest tube.

Circulation
- Assess pulses.
- Control active bleeding. Splint long-bone deformity/fracture.
- Secure IV access.
- Administer fluids or blood to unstable patients.

Disability
- Assess GCS and gross motor/sensory function in extremities.

Exposure
- Disrobe patient and inspect for additional injuries.
- Cover patient after primary survey to avoid hypothermia.

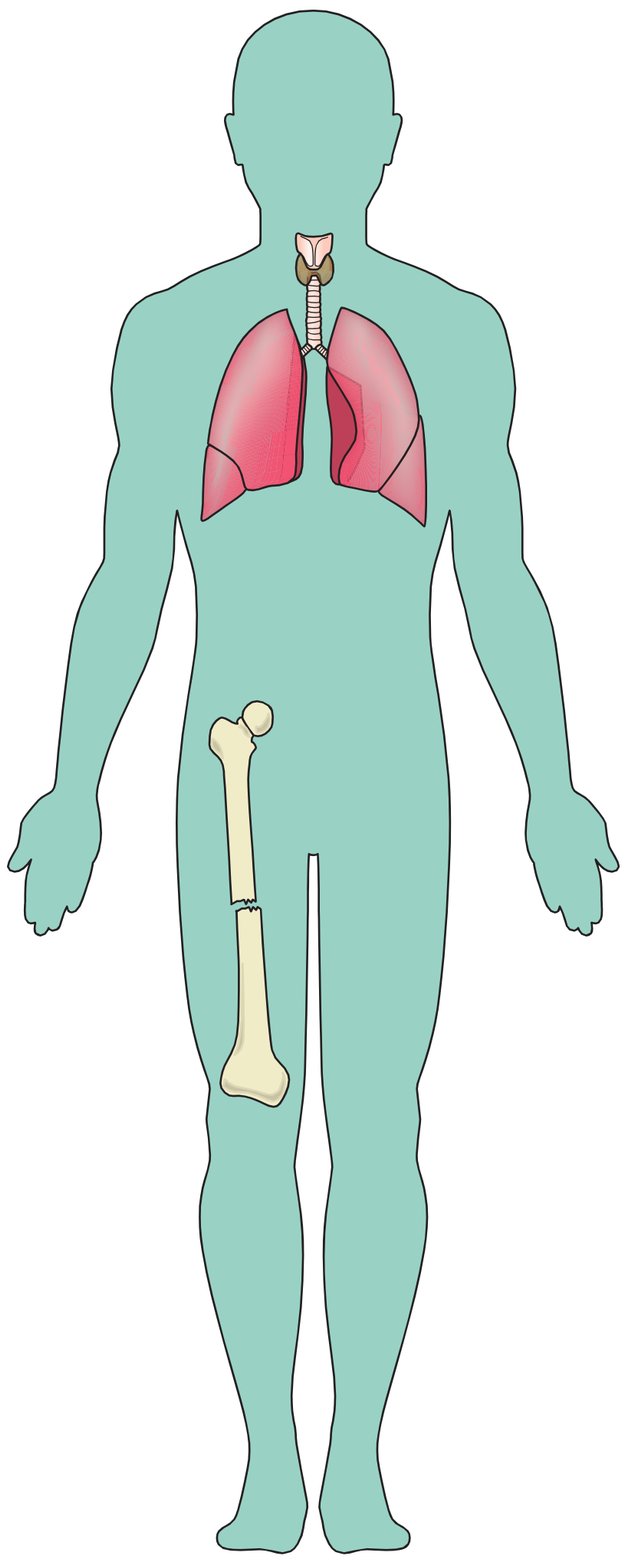


FIGURE 2.17-1. Primary trauma survey.

KEY FACT

Classic triad of cardiac tamponade includes muffled heart sounds, jugular venous distention, and hypotension.

KEY FACT

A rough estimate of systolic BP (SBP) can be made on the basis of palpated pulses. Carotids correspond roughly to an SBP of 60 mm Hg, femorals to an SBP of 70 mm Hg, and radials to an SBP of 80 mm Hg.

KEY FACT

Suspect urethral injury in the presence of blood at the urethral meatus, perineal ecchymosis, blood in the scrotum, a high-riding/nonpalpable prostate, or a pelvic fracture. A retrograde urethrogram can confirm urethral integrity.



FIGURE 2.17-2. Tension pneumothorax. Note the hyperlucent left hemithorax, flattening and inferior displacement of the left diaphragm, and rightward shift of the mediastinal structures. These are typical radiographic findings in patients with tension pneumothorax.

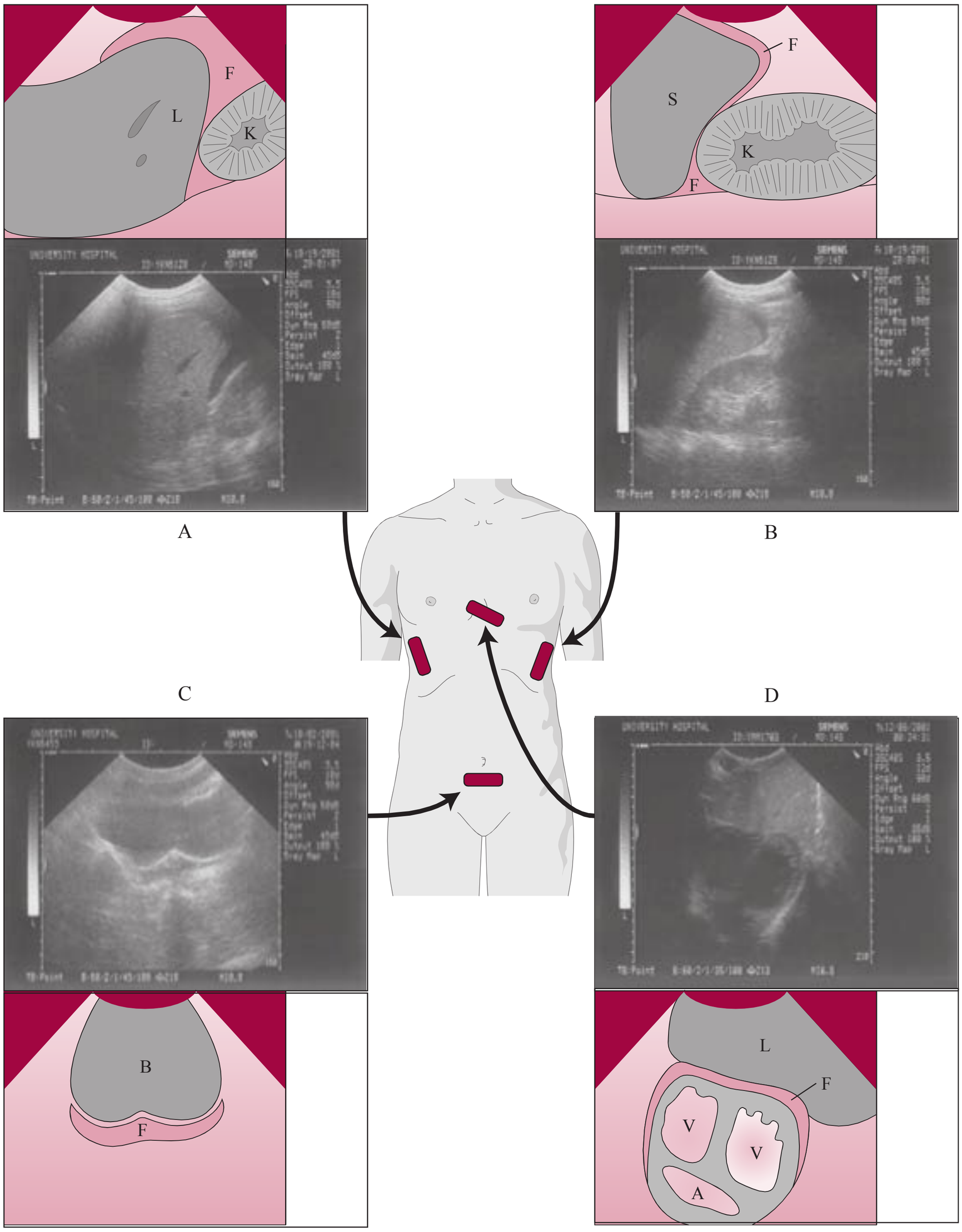


FIGURE 2.17-3. Focused abdominal sonography for trauma (FAST exam). Illustration of the four views for the FAST exam and where fluid would be seen in each view. (A) atrium; (B) bladder; (F) fluid; (K) kidney; (L) liver; (S) spleen; (V) ventricle. (Reproduced with permission from Stone CK, Humphries RL, eds. Current Diagnosis and Treatment: Emergency Medicine, 7th ed. New York, NY: McGraw-Hill; 2011.)

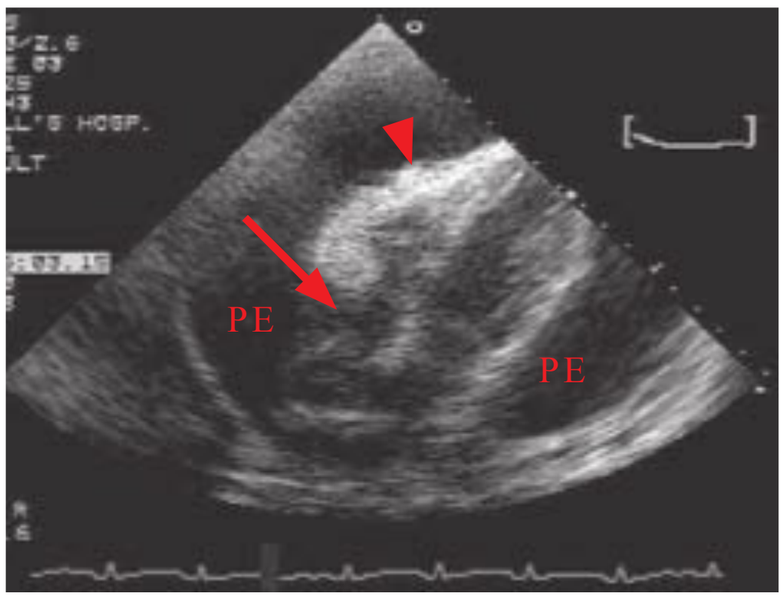


FIGURE 2.17-4. Cardiac tamponade. Echocardiogram in a patient with cardiac tamponade shows a large pericardial effusion (PE) with right atrial (arrow) and right ventricular (arrowhead) collapse. (Reproduced with permission from Hall JB et al. Principles of Critical Care, 3rd ed. New York, NY: McGraw-Hill; 2005.)

Penetrating Trauma

Evaluation and treatment of penetrating trauma depend on the location and extent of the injury.

NECK

- All wounds that violate the platysma are considered true penetrating neck trauma.
- Intubate these patients early before the airway becomes more compromised.
- Immediate surgical exploration of neck wounds is indicated if shock and active hemorrhage are present.
- Appropriate tests may include angiography of the aorta and carotid/cerebral arteries, CT scan of the neck with or without CT angiography, Doppler ultrasonography, contrast esophagogram, esophagoscopy, or bronchoscopy. Approach should be guided by mechanism of injury and patient presentation.

CHEST

- Unstable patients with penetrating thoracic injuries require immediate **intubation** followed by assessment and treatment of the life-threatening injuries described above. Empiric placement of bilateral chest tubes may be needed if the precise nature of injury is unclear.
- Consider in differential: Tension pneumothorax, open pneumothorax, hemothorax, flail chest and pulmonary contusion, cardiac tamponade, aortic disruption, diaphragmatic tear, and esophageal injury.
- Open thoracotomy to rule out pericardial effusion may be indicated for patients with penetrating chest trauma and cardiac arrest, **provided that the cardiac arrest occurred in front of medical personnel in the ED or shortly before arrival.**
- Leave impaled objects in place until the patient is taken to the OR, as such objects may tamponade further blood loss.
- If a previously stable chest trauma patient becomes rapidly unstable, suspect **air embolism.**
- A new diastolic murmur after chest trauma suggests **aortic dissection.**

Q

A 19-year-old man is brought to the ED after sustaining a gunshot wound to the chest. On arrival, he has a BP of 60/30 mm Hg, ↓ breath sounds on the left side, distended neck veins, and tracheal deviation to the right side. What is the most appropriate next step in management?

ABDOMEN

- The absence of pain does not rule out an abdominal injury.
- Gunshot wounds below the fourth intercostal space (level of the nipple) usually require immediate exploratory laparotomy.
- Stab wounds in a hemodynamically unstable patient or in a patient with peritoneal signs or evisceration require immediate exploratory laparotomy.
- Penetrating stab wounds in a stable patient warrant a CT and close follow-up.
- Diagnostic peritoneal lavage in the evaluation of blunt abdominal trauma has been largely replaced with ultrasound or CT; however, it may be useful in settings of equivocal results or in resource-poor settings.

MUSCULOSKELETAL

- Neurovascular assessment is critical; check pulses, motor function, and sensory function.
- Arteriography and surgical management are required for suspected vascular injuries.
- Nerve injuries generally require surgical repair.
- **Early wound irrigation** and **tissue debridement,** not antibiotic therapy, are the most important steps in the treatment of contaminated wounds. However, do administer antibiotics and **tetanus prophylaxis.**

Blunt and Deceleration Trauma

HEAD

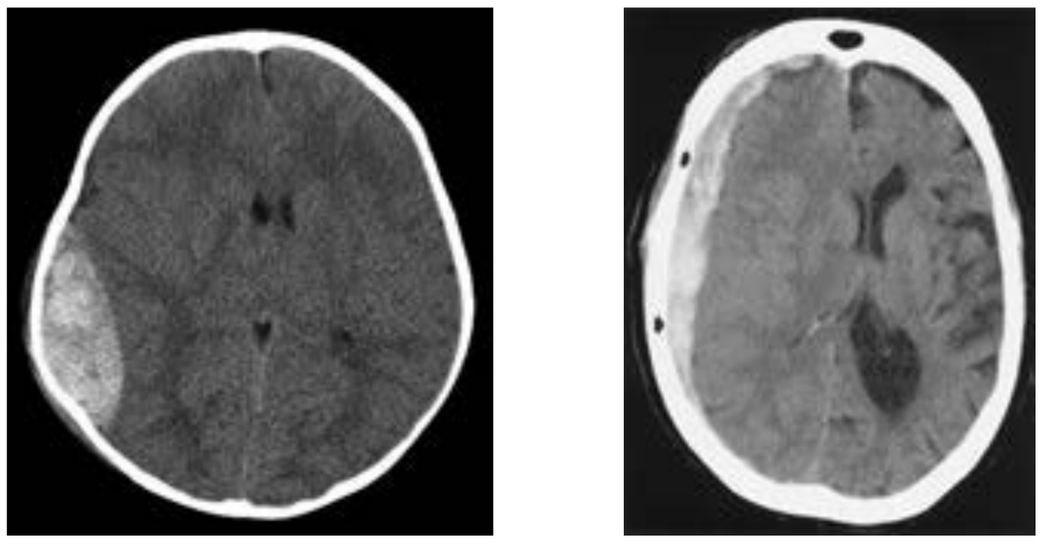
- Look for signs of ↑ ICP such as bradycardia, hypertension, respiratory depression, fixed and dilated pupil(s), vomiting, and/or papilledema. Treat ↑ ICP with head elevation, hyperventilation, and IV mannitol. Consider surgical decompression.
- A rapid-deceleration head injury causes **coup-contrecoup** injuries, in which bleeding is noted both at the site of impact and across from the point of impact.
- Diffuse axonal injury often occurs with rapid-deceleration head injuries. CT characteristically shows **blurring and punctate hemorrhaging along the gray–white matter junction.** Reduce 2° injury by limiting cerebral edema and increases in ICP.
- **Epidural hematomas:** Lenticular or biconvex in shape on head CT (see Figure 2.17-5A). The hemorrhage is often from the middle meningeal artery (the higher arterial pressure is able to push the dura away from the skull, causing the lens shape on imaging). These hemorrhages **cannot cross suture lines** but can expand rapidly and cause herniation and death. Patients classically have loss of consciousness immediately after the injury and then have a **"lucid interval,"** after which they become comatose. Examination may show ipsilateral blown pupil and ipsilateral hemiparesis. Emergent craniotomy is needed.
- **Subdural hematomas:** Follow the curve of the skull and result from damage to the dural bridging veins (see Figure 2.17-5B). These hemorrhages **can cross suture lines.** They may present acutely (immediate), subacutely (days), or chronically (weeks).

KEY FACT

Marfan syndrome, syphilis, and Ehlers-Danlos syndrome all predispose to a weak aortic wall.

A

Insert a 14-gauge IV angiocatheter into the second intercostal space at the midclavicular line to achieve emergent decompression of the tension pneumothorax. Then place a chest tube.



A B

FIGURE 2.17-5. Acute epidural and acute subdural hematoma. (A) Noncontrast CT showing a right temporal acute epidural hematoma. Note the characteristic **biconvex** shape. **(B)** Noncontrast CT demonstrating a right acute holohemispheric subdural hematoma. Note the characteristic **crescentic** shape. (Part A reproduced with permission from Doherty GM. Current Diagnosis & Treatment: Surgery, 13th ed. New York, NY: McGraw-Hill; 2010. Part B reproduced with permission from Chen MY et al. Basic Radiology, 1st ed. New York, NY: McGraw-Hill; 2004.)

CHEST

- Tracheobronchial disruption is most often caused by deceleration shearing forces. Physical findings include respiratory distress, hemoptysis, sternal tenderness, and subcutaneous emphysema. Radiographs may show a large pneumothorax or pneumomediastinum (see Figure 2.17-6).
- Blunt cardiac injury (aka myocardial contusion) may present as a new bundle branch block, ectopy or dysrhythmia, or hypotension. Serum cardiac biomarkers are often elevated. Intervention is rarely required.
- Pulmonary contusion may lead to hypoxia due to damage to capillaries and leakage of intra- and extravascular fluid. Hypoxia tends to worsen with fluid hydration. Look for patchy alveolar opacities on CXR. Maintain adequate ventilation and control pain. More common in children because of a less rigid, protective chest wall.

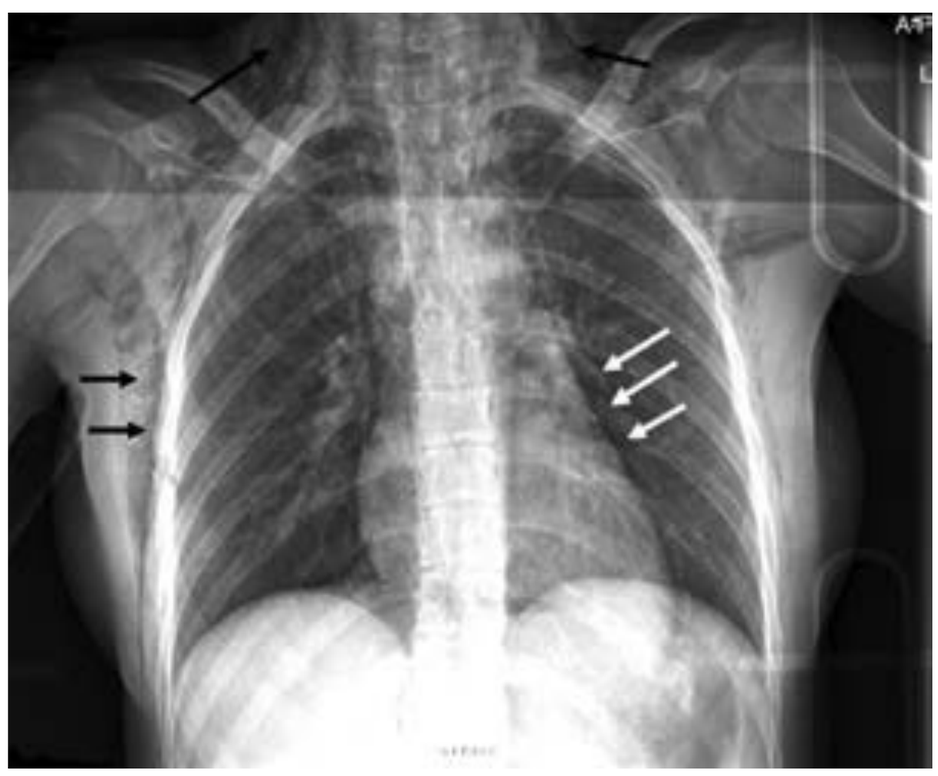


FIGURE 2.17-6. X-ray of the chest reveals pneumomediastinum (white arrows) and subcutaneous emphysema (black arrows). (Reproduced with permission from Van Heijl M et al. Unique case of esophageal rupture after a fall from height, BMC Emerg Med 2009 Dec 15;9:24.)

Q 1

A 25-year-old man walks into the ED holding a blood-soaked towel against his neck after being stabbed by his girlfriend. The patient is calm, and his vital signs are stable. Physical examination reveals that the knife wound extends through the platysma muscle. What is the next step in management?

Q 2

A 10-year-old boy is brought to the ED 5 hours after he hit his head on a concrete sidewalk after falling off his skateboard. He briefly lost consciousness at the scene, but his neurologic exam and head CT are normal. What is the next step in ED management?

KEY FACT

Aortic disruption is often associated with first and second rib, scapular, and sternal fractures.

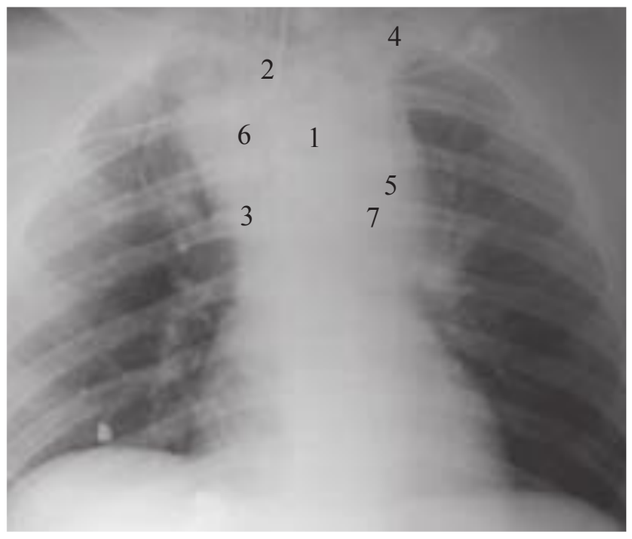


FIGURE 2.17-7. Aortic disruption. X-ray of the chest of hypotensive man injured in a high-speed motor vehicle collision. Findings: (1) widened mediastinum; (2) deviation of the trachea to the right; (3) widening of the right paratracheal stripe; (4) left apical cap; (5) blurring of the aortic knob; (6) deviation of the NG tube to the right; (7) obliteration of the aortopulmonary window. (Reproduced with permission from Stone CK, Humphries RL. Current Diagnosis & Treatment: Emergency Medicine, 7th ed. New York, NY: McGraw Hill; 2011.)

1 A

Admit the patient for surgical consultation and possible exploration of the wound. All penetrating trauma that violates the platysma muscle mandates admission and surgical consultation for surgery or further diagnostic evaluation.

2 A

Discharge the patient. If the head CT is normal, patients with mild to moderate head injuries can be discharged with instructions to return immediately if neurologic symptoms develop.

Aortic Disruption

Classic cause is a **rapid-deceleration injury** (eg, high-speed motor vehicle accidents, ejection from vehicles, falls from heights). Since complete aortic rupture is rapidly fatal (85% die at the scene), patients with aortic disruption seen in the ED usually have a contained hematoma within the adventitia. Laceration is most common just proximal to the ligamentum arteriosum.

Diagnosis

- Possible clinical findings include upper extremity hypertension and a hoarse, quiet voice from impingement of the recurrent laryngeal nerve.
- **CXR** reveals a **widened mediastinum** (> 8 cm), **loss of aortic knob, pleural cap,** deviation of the trachea and esophagus, and depression of the left main stem bronchus (Figure 2.17-7).
- Ultrasonography can help with diagnosis of concurrent pericardial tamponade.
- If patient is stable, CT should be obtained to confirm suspicious CXR findings. Can be done if patient is unstable for CT.

Treatment

Basic trauma management (ABCs); emergent surgery for any defect repair.

Flail Chest

Three or more adjacent ribs fractured at two points, causing paradoxical inward movement of the segment with inspiration (Figure 2.17-8).

History/Pe

Presents with crepitus and abnormal chest wall movement. Abnormal chest wall movement may not be appreciated if the patient is splinting because of pain.

Diagnosis

Primarily clinical, although CXR and O_2 saturation are helpful.

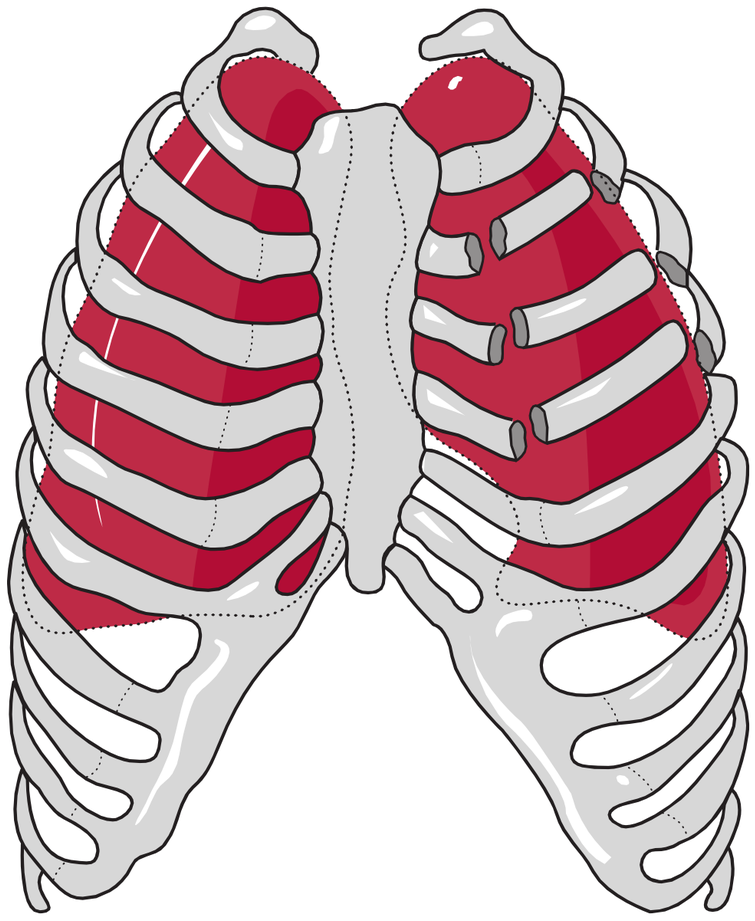


FIGURE 2.17-8. Flail chest. (Reproduced with permission from Doherty GM. Current Diagnosis & Treatment: Surgery, 13th ed. New York, NY: McGraw-Hill; 2009.)

Treatment

- **O_2; narcotic analgesia.**
- **Respiratory support,** including intubation and positive-pressure mechanical ventilation, may be needed to treat hypoxemia. **Surgical fixation** of the chest wall is generally needed.

Complications

Respiratory compromise is a complication due to underlying pulmonary contusion.

ABDOMEN/PELVIS

- The **spleen** is the **most commonly injured organ following blunt abdominal trauma,** with **liver** and **hollow viscus** injuries following in descending order. Symptoms are consistent with signs of blood loss and include hypotension, tachycardia, and peritonitis. Suspect spleen or liver injury when lower rib fractures are present.
- The duodenum is susceptible to compression injury as a result of its position in front of the spine. Look for retroperitoneal air on AXR, and confirm the diagnosis with CT, which can also rule out a duodenal hematoma.
- Pancreatic injury or bowel hematoma should be suspected after a direct epigastric blow (handlebar injury).
- **Diaphragmatic rupture** may occur with blunt or penetrating trauma. **Kehr sign** may be present; radiographs may demonstrate an elevated hemidiaphragm or abdominal viscera in the thorax.
- The **kidneys** are the **most commonly injured GU organ in trauma,** with injuries including renal contusion, laceration, fracture, and pedicle injury.
- In hemodynamically stable patients, abdominal blunt trauma can be diagnosed with FAST scan, CT scan, and serial abdominal exams.
- In hemodynamically unstable patients, abdominal blunt trauma should be treated with immediate exploratory laparotomy to look for organ injury or intra-abdominal bleeding.

Pelvic Fractures

Most commonly occur after high-speed traumas such as motor vehicle accidents or falls from heights. Require prompt stabilization with an external binder and surgical evaluation by a trauma or orthopedic surgeon in light of the potential for life-threatening hemorrhage.

Diagnosis

- May present with an unstable pelvis upon manipulation.
- Pelvic x-ray films may confirm the fracture; in a stable patient, a CT scan of the pelvis will better define the extent of injury.
- If hypotension and shock are present, an exsanguinating hemorrhage is likely. An external pelvic binder should be used to splint the fracture and limit blood loss.

Treatment

- Provide resuscitation early. More than 40% of patients with pelvic fractures require transfusion.

KEY FACT

Kehr sign: Free blood in the abdomen may lead to referred pain to the shoulder as a result of irritation to the diaphragm, which is innervated by the phrenic nerve that shares origins with the brachial plexus.

KEY FACT

Unstable patients with abdominal trauma should undergo immediate exploratory laparotomy.

KEY FACT

Look for characteristic "seat belt signs" in restrained passengers to assess for possible abdominal organ injury due to deceleration against a taut seat belt (Figure 2.17-9).



FIGURE 2.17-9. Seat belt sign. Adult restrained driver with abdominal seat belt sign. (Reproduced with permission from Abbas AK, Hefny AF, Abu-Zidan FM. Seatbelts and road traffic collision injuries, World J Emerg Surg 2011 May 28;6(1):18.)

KEY FACT

As a result of the ringlike structure of the pelvic anatomy, pelvic fractures tend to occur in multiples rather than singular fractures.

- Consider emergent external pelvic fixation and angiography with embolization of bleeding vessels. Internal pelvic fixation can be considered in a hemodynamically stable patient.
- Pelvic injuries can be associated with urethral injury suggested by **blood at urethral meatus or in the scrotum; a high-riding, "ballotable" prostate;** or a **nonpalpable prostate.**
- **Retrograde urethrogram** should rule out suspected injury before a Foley catheter is placed.

MNEMONIC

Possible causes of PEA—

The 5 H's and 5 T's

Hypovolemia
Hypoxia
Hydrogen ion: acidosis
Hyper/**H**ypo: K^+, other metabolic
Hypothermia
Tablets: drug overdose, ingestion
Tamponade: cardiac
Tension pneumothorax
Thrombosis: coronary
Thrombosis: pulmonary embolism

Cardiac Life Support Basics

Table 2.17-2 summarizes the basic management of cardiac arrhythmias in an acute setting.

Acute Abdomen

Acute-onset abdominal pain has many potential etiologies and may require immediate medical or surgical intervention. Sharp, focal pain with tenderness and guarding generally implies a parietal (peritoneal) etiology; dull, crampy, achy, and midline or diffuse pain is commonly of visceral (organ) origin. Patients with parietal pain generally prefer immobility, whereas those with visceral pain are often unable to lie still. Figure 2.17-10 identifies common causes of acute abdomen.

TABLE 2.17-2. Management of Cardiac Arrhythmias[a,b]

Arrhythmia	Treatment
Asystole or PEA	Initiate CPR. Give epinephrine or vasopressin; simultaneously search for the underlying cause (see the **5 H's and 5 T's** mnemonics) and provide empiric treatment.
Ventricular fibrillation or pulseless ventricular tachycardia	Initiate CPR. Defibrillate with 120–200 J (biphasic) immediately → defibrillate again → epinephrine → defibrillate → amiodarone → defibrillate → epinephrine.
SVT	If unstable, perform synchronized electrical cardioversion. If stable, control rate with vagal maneuvers (Valsalva maneuver, carotid sinus massage, or cold stimulus). If resistant to maneuvers, give adenosine followed by other AV-nodal blocking agents (CCBs or β-blockers) if rhythm fails to convert.
Atrial fibrillation (AF)/ flutter	If unstable, perform synchronized electrical cardioversion at 120–200 J (biphasic). If stable, control rate with diltiazem or β-blockers and anticoagulate if duration is > 48 hours. Elective cardioversion may be performed if duration is < 48 hours; otherwise, the clinician must anticoagulate or perform TEE prior to conversion. Do not give nodal blockers if there is evidence of Wolff-Parkinson-White syndrome (δ waves) on ECG. Use procainamide instead.
Bradycardia	If symptomatic, give atropine. If ineffective, use transcutaneous pacing, dopamine, or epinephrine.

[a]In all cases, disruptions of CPR should be minimized. After a shock or administration of a drug, CPR should be resumed immediately, and 5 cycles of CPR should be given before checking for a pulse or rhythm. "→" above represents 5 cycles of CPR followed by a pulse or rhythm check.

[b]Doses of electricity listed above assume a biphasic defibrillator.

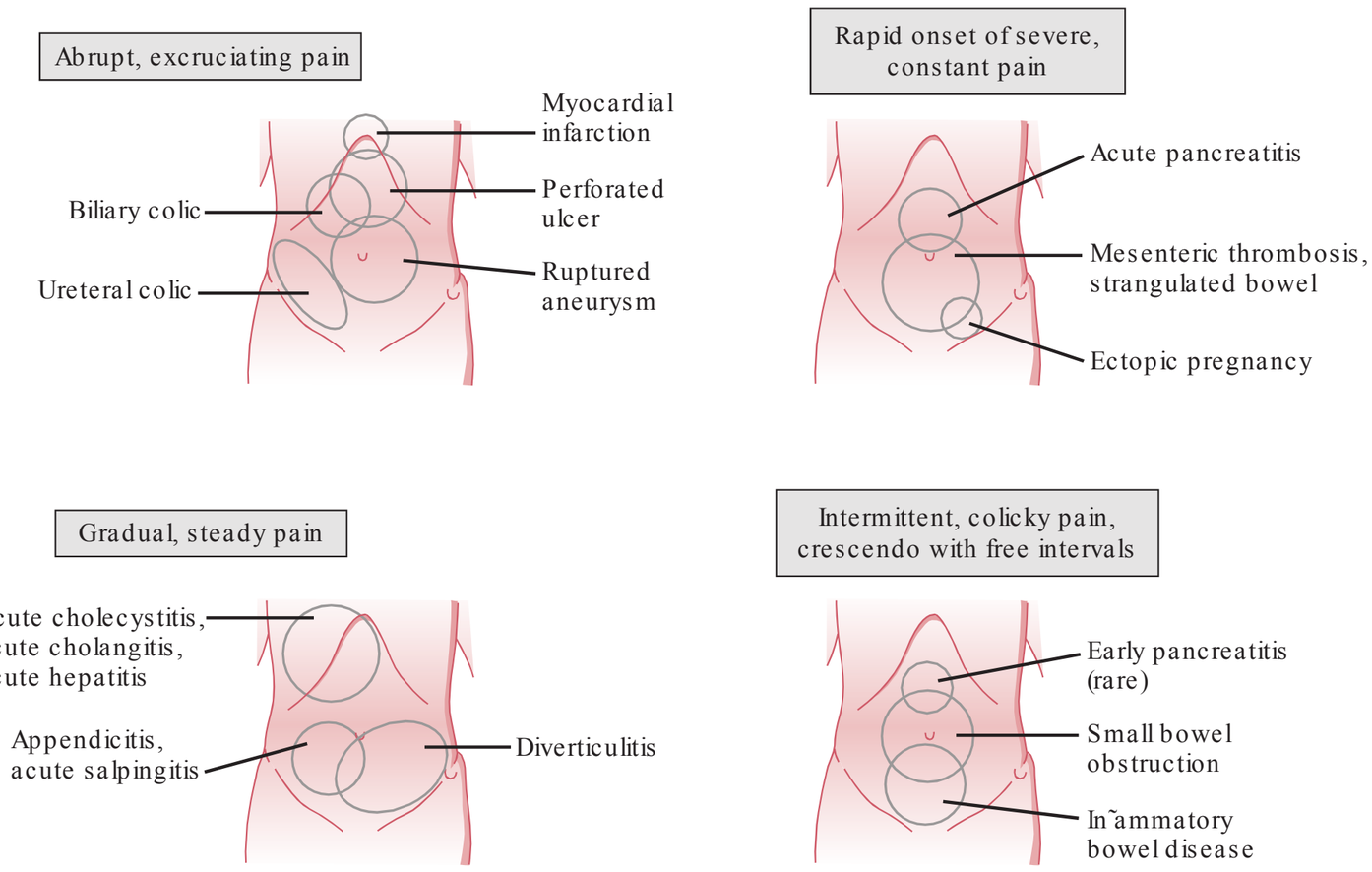


FIGURE 2.17-10. Acute abdomen. The location and character of pain are helpful in the differential diagnosis of the acute abdomen. (Reproduced with permission from Doherty GM et al. Current Diagnosis & Treatment: Surgery, 13th ed. New York, NY: McGraw-Hill; 2010.)

History/Pe

- Pay careful attention to the historical features in the acute abdominal presentation.
- Consider the gynecologic history in women (including last menstrual period, pregnancy, and any STD symptoms). If a patient has abdominal pain with cervical motion tenderness, there should be a low threshold to treat for **pelvic inflammatory disease (PID).**
- **Perforation** leads to sudden onset of diffuse, severe pain, usually with abdominal rigidity.
- **Obstruction** leads to acute onset of severe, radiating, colicky pain. Patients may complain of obstipation (failure to pass stool or gas) or bilious emesis. Think of small bowel obstruction in patients with a history of abdominal surgeries.
- **Inflammation** leads to gradual onset (over 10–12 hours) of constant, ill-defined pain.
- **Associated symptoms** include the following:
  - Anorexia, nausea, vomiting, changes in bowel habits, hematochezia, and melena suggest GI etiologies.
  - Fever and cough suggest pneumonia.
  - Hematuria, pyuria, and costovertebral angle tenderness point to a GU etiology.
- If associated with meals, consider mesenteric ischemia (especially in the elderly or those with coronary or peripheral artery disease risk factors), peptic ulcer disease, biliary disease, pancreatitis, or bowel pathology.
- A family history of abdominal pain may indicate familial Mediterranean fever or acute intermittent porphyria.

Diagnosis

- In the presence of peritoneal signs, shock, or impending shock, emergent exploratory laparotomy is necessary.
- If the patient is stable, a complete physical examination—including a **rectal examination** and, in women, a **pelvic examination**—is mandatory.

KEY FACT

A ⊕ β-human chorionic gonadotropin (β-hCG) in the setting of shock is a ruptured ectopic pregnancy until proven otherwise.

KEY FACT

Pneumonia can cause right/left upper quadrant abdominal pain due to diaphragmatic irritation.

Q 1

A 22-year-old woman is brought to the ED after a motor vehicle collision in which she was the restrained driver. She receives 2 L of crystalloid en route and has a BP of 65/40 mm Hg and a heart rate of 135 bpm on arrival. She has ↓ breath sounds on the right, flat neck veins, and dullness to percussion on the right side. What is the most likely diagnosis?

Q 2

A 36-year-old man is brought to the ED following a motor vehicle collision in which he was an unrestrained passenger. X-ray films show multiple fractures. Several hours later he develops fever, respiratory distress, and a rash consisting of small red and purple 1- to 2-mm macules covering his arms and shoulders. What is the most likely diagnosis?

Q 3

A 65-year-old male smoker is brought to the ED for sudden-onset abdominal and back pain. The anxious patient complains of "ripping pain." Physical examination reveals a large, pulsatile mass behind the umbilicus. The patient's BP is 80/50 mm Hg and heart rate 125 bpm. You begin crystalloid and blood infusions. What is the most appropriate next step in management?

KEY FACT

Think of ischemic colitis in an elderly patient with a history of AF or recent AAA repair, or bloody stool, with sudden-onset abdominal pain out of proportion to physical findings.

KEY FACT

All women with an acute abdomen require a pelvic exam, pregnancy test, and pelvic ultrasonography to rule out emergencies (eg, ectopic pregnancy, ovarian torsion) and to distinguish from more common causes (eg, PID).

1 A

Hemothorax. Three important clues to look for are ↓ or absent breath sounds on the affected side, no chest movement with respiratory effort, and dullness to percussion on the affected side. Each hemithorax can hold 40% of a patient's circulating blood volume, and patients may therefore present in hypovolemic shock.

2 A

Fat embolism. The classic presentation of fat embolism is fever, tachypnea, tachycardia, conjunctival hemorrhage, and upper extremity petechiae after a patient suffers long-bone fractures.

3 A

On the basis of the clinical findings of shock, abdominal pain, and a pulsatile mass, the patient has a ruptured AAA, which is a surgical emergency. If patient is stable, ultrasonography or urgent CT can confirm aneurysm and inform intervention; however, immediate laparotomy or endovascular repair should not be delayed.

- Obtain electrolytes, LFTs, lipase, **urine or serum β-hCG,** UA, and a CBC with differential.
- Consider an upright CXR for suspected perforation or pulmonary pathology. AXR may be useful for obstruction (air-fluid levels, distended loops of bowel) or perforation (free air under the diaphragm; see Figure 2.17-11), but CT is more sensitive and specific.
- CT is used to diagnose appendicitis, diverticulitis, abscess, renal stones, AAA, obstruction.
- Ultrasonography is helpful for diagnosing cholecystitis and gynecologic pathology and can diagnose hemoperitoneum and AAA in unstable patients.

Treatment

- **Hemodynamically unstable patients must have emergent surgical management.**
- In stable patients, expectant management may include NPO status, NG tube placement (for decompression of bowel in the setting of obstruction or acute pancreatitis), IV fluids, placement of a Foley catheter (to monitor urine output and fluid status), and vital sign monitoring with serial abdominal examinations and serial labs.
- Broad-spectrum antibiotics for patients with perforation or signs of sepsis. May be indicated for patients with infectious processes such as cholecystitis, diverticulitis, and pyelonephritis.
- Type and cross all unstable patients and those in whom you suspect potential hemorrhage.

Acute Appendicitis

The inciting event is obstruction of the appendiceal lumen with subsequent inflammation and infection. Rising intraluminal pressure leads to vascular compromise of the appendix, ischemia, necrosis, and possible perforation. Etiologies include hypertrophied lymphoid tissue (55–65%), fecalith (35%), foreign body, tumor (eg, carcinoid tumor), and parasites. Incidence peaks in the early teens (most patients between 10 and 30 years of age), and the male-to-female ratio is 2:1.



FIGURE 2.17-11. Pneumoperitoneum. X-ray of the chest showing multiple small bowel perforations from CMV ileitis in a young man infected with HIV. (Reproduced with permission from Michalopoulos N et al. Small bowel perforation due to CMV enteritis infection in an HIV-positive patient, BMC Res Notes 2013 Feb 4;6:45.)

History/Pe

- Classically presents with dull periumbilical pain lasting 1–12 hours that leads to sharp RLQ pain at McBurney point.
- Can present with nausea, vomiting, anorexia, and low-grade fever.
- Psoas, obturator, and Rovsing signs are not sensitive tests, but their presence ↑ the likelihood of appendicitis.
- In **perforated appendix,** partial pain relief is possible, but peritoneal signs (eg, rebound, guarding, hypotension, ↑ WBC count, fever) will ultimately develop.
- Children, the elderly, pregnant women, and those with retrocecal appendices may have atypical presentations that may result in misdiagnosis and ↑ mortality.

Diagnosis

- Diagnosed by clinical impression.
- Look for fever, mild leukocytosis (11,000–15,000 cells/μL) with left shift, and UA with a few RBCs and/or WBCs.
- If the clinical diagnosis is unequivocal, no imaging studies are necessary. Otherwise, studies include the following:
  - **CT scan with PO and IV contrast (95–98% sensitive):** Periappendiceal stranding or fluid; enlarged appendix (see Figure 2.17-12).
  - **Ultrasonography:** An enlarged, noncompressible appendix. Preferred for children and pregnant women.

Treatment

- The patient should be NPO and receive IV hydration, analgesia, antiemetics, and antibiotics with anaerobic and gram-⊖ coverage.
- Immediate open or laparoscopic appendectomy is the definitive treatment. If appendicitis is not found, complete exploration of the abdomen is performed.
- **Perforation:** Administer antibiotics until the patient is afebrile with a normalized WBC count; the wound should be closed by delayed 1° closure.
- **Abscess:** Treat with broad-spectrum antibiotics and percutaneous drainage; an elective appendectomy should be performed 6–8 weeks later.

KEY FACT

McBurney point is located one-third of the distance from the anterior superior iliac spine to the umbilicus.

KEY FACT

- **"Hamburger sign":** If a patient wants to eat, consider a diagnosis other than appendicitis.
- **Psoas sign:** Passive extension of the hip leading to RLQ pain.
- **Obturator sign:** Passive internal rotation of the flexed hip leading to RLQ pain.
- **Rovsing sign:** Deep palpation of the LLQ leading to RLQ pain.

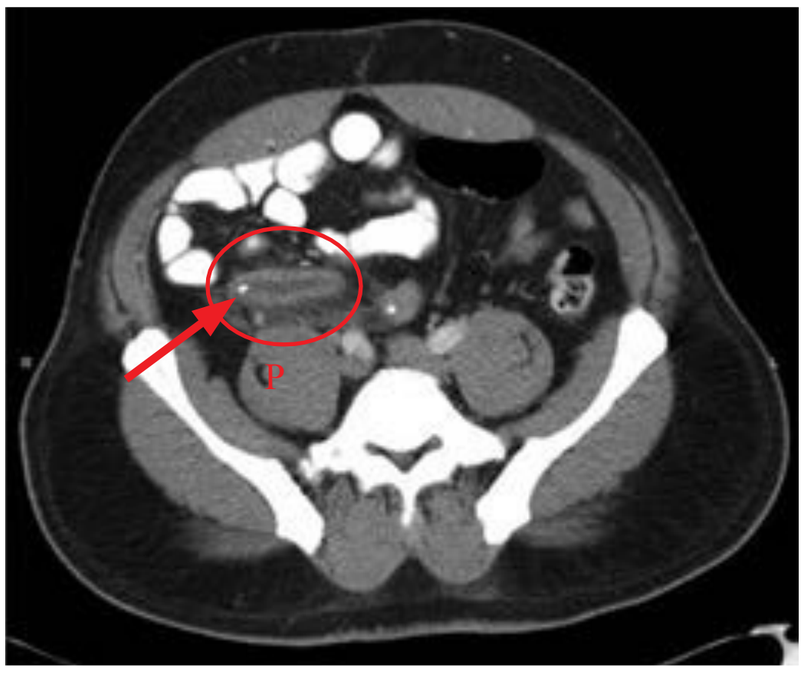


FIGURE 2.17-12. Acute appendicitis. Contrast-enhanced CT image through the lower abdomen in a 30-year-old woman with RLQ pain demonstrates an enlarged, hyperenhancing appendix (circle) with periappendiceal fat stranding located just anterior to the right psoas muscle (P). An appendicolith (arrow) is noted near the base of the appendix. (Reproduced with permission from USMLE-Rx.com.)

Burns

A **leading cause of death in children.** Patients with serious burns should be treated in an ICU setting. Burns can be chemical, electrical, or thermal, and are categorized by depth of tissue destruction (see Figure 2.17-13):

- **First degree:** Only the epidermis is involved. The area is painful and erythematous, but blisters are not present, and capillary refill is intact. Looks like a sunburn.
- **Second degree:** The epidermis and partial thickness of the dermis are involved. The area is painful, and blisters are present.
- **Third degree:** The epidermis, the full thickness of the dermis, and potentially deeper tissues are involved. The area is painless, white, and charred.

History/Pe

- Patients may present with obvious skin wounds, but significant deep destruction may not be visible, especially with electrical burns.
- Conduct a thorough airway and lung examination to assess for inhalation injury.
- Maintain a high index of suspicion for carbon monoxide poisoning in patients with inhalation injury or involvement in a closed-space fire.
- Consider cyanide poisoning in closed-space fires with burning carpets and textiles.

Diagnosis

- Assess ABCs. If evidence of thermal or inhalation injury to the upper airway, intubate.
- Be vigilant for shock, inhalation injury, and carbon monoxide poisoning. Obtain a CXR and a carboxyhemoglobin level.
- Evaluate the percentage of BSA (% BSA) involved (see Figure 2.17-14).

Treatment

- Supportive measures; tetanus, stress ulcer prophylaxis, and IV narcotic analgesia.
- For second- and third-degree burns, fluid repletion using the **Parkland formula** is critical; adjust repletion on the basis of additional insensible losses to maintain at least 1 cc/kg/hr of urine output.

KEY FACT

Use the "rule of 9's" to estimate % (count only second- and third-degree burns).

Body surface area (BSA) in adults:
Head and each arm = 9%
Back and chest each = 18%
Each leg = 18%
Perineum = 1%
*Patient's palm (including fingers) represents about 1% of total BSA in adults and children.

KEY FACT

Parkland formula: Fluids for the first 24 hours = 4 × patient's weight in kg × % BSA. Give 50% of fluids over the first 8 hours and the remaining 50% over the following 16 hours.

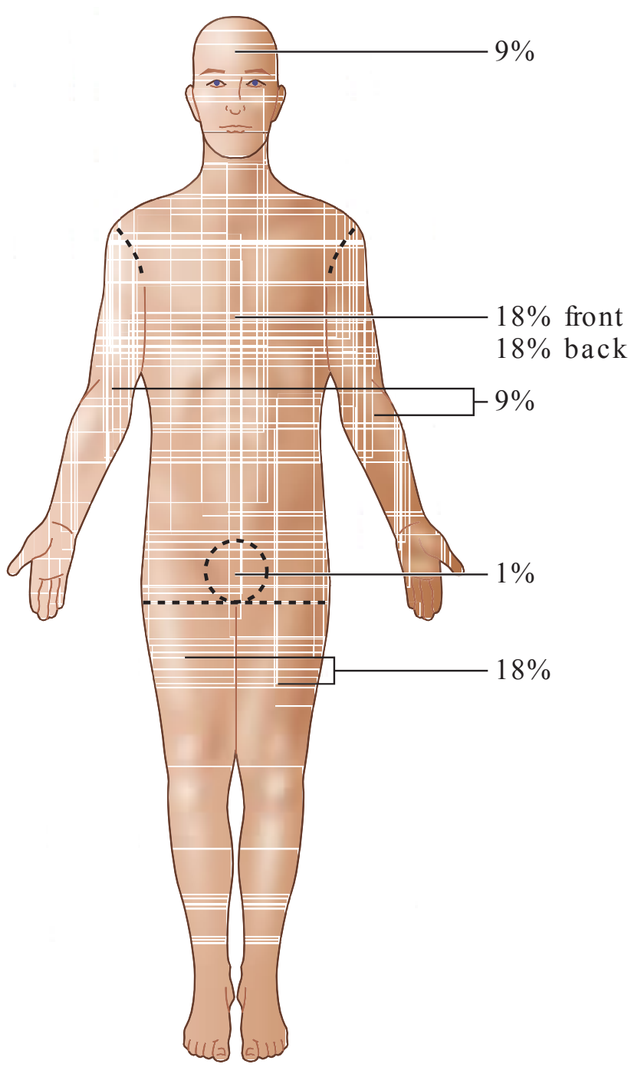


FIGURE 2.17-14. The rule of 9's in the estimation of BSA. Estimation of BSA is imperative in the evaluation of burn victims. (Reproduced with permission from Ma OJ et al. Emergency Medicine Manual, 6th ed. New York, NY: McGraw-Hill; 2004.)

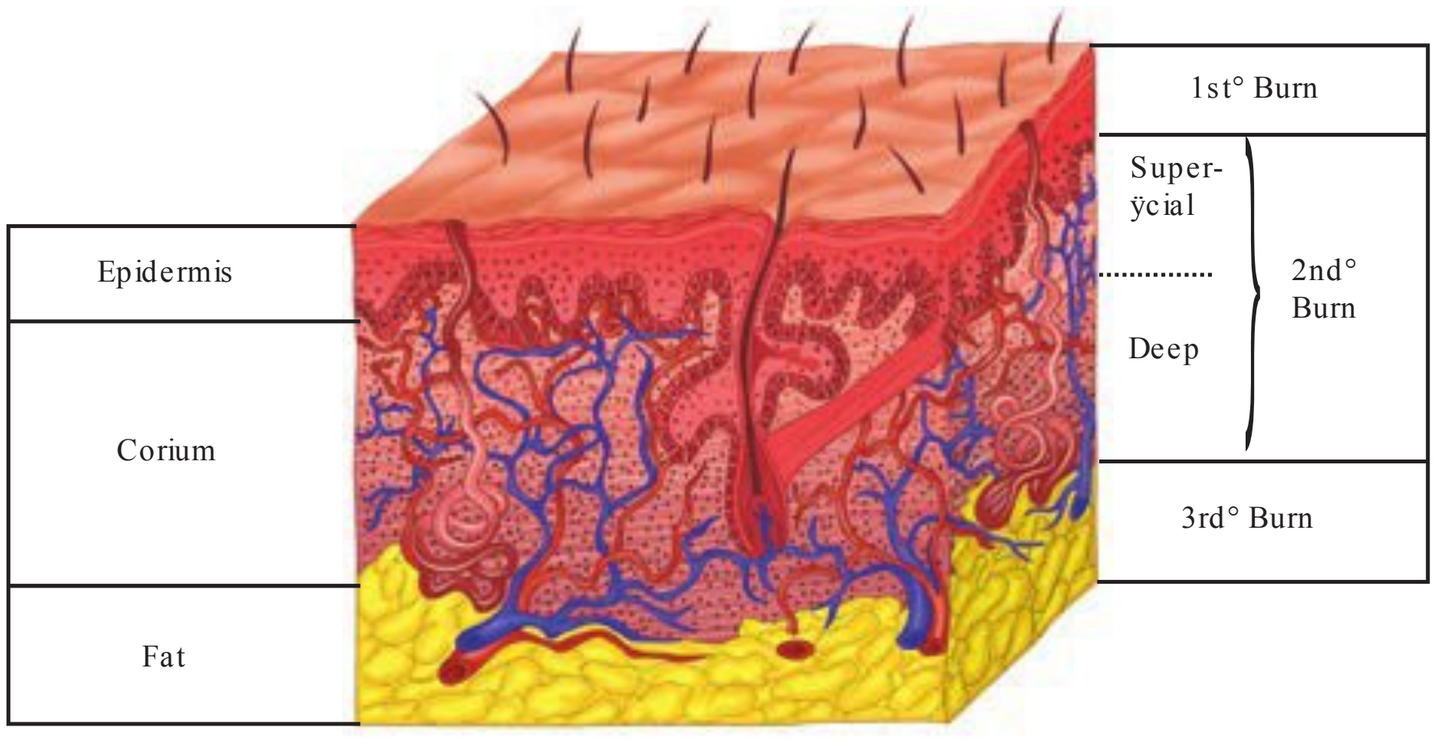


FIGURE 2.17-13. Depth of burn wounds. (Reproduced with permission from Strange GR et al. Pediatric Emergency Medicine, 3rd ed. New York, NY: McGraw-Hill; 2009.)

- Topical antimicrobials (eg, silver sulfadiazine) can be used prophylactically when the epidermis is no longer intact; however, there is no proven benefit associated with the use of PO/IV antibiotics or corticosteroids.

Complications

- Shock, compartment syndrome (due to stricture), and superinfection (most likely due to Pseudomonas or gram-⊕ cocci).
- Criteria for transfer to a burn center include the following:
  - Partial-thickness and full-thickness burns > 10% BSA in patients < 10 years or > 50 years of age.
  - Partial-thickness and full-thickness burns > 20% BSA in other age groups.
  - Any full- or partial-thickness burn over critical areas (face, hands, feet, genitals, perineum, major joints).
  - Circumferential burns; chemical, electrical, or lightning injury; inhalation injury.
  - Any special psychosocial or rehabilitative care needs.

Postoperative Fever

- Occurs in 40% of all postoperative patients. Remember the mnemonic "**W**ind, **W**ater, **W**ounds, **W**alking, and **W**onder drugs." Another **"W"** of postoperative fever is "**W**omb" in OB/GYN (Table 2.17-3).
- ↓ the risk of postoperative fever with incentive spirometry, pre- and postoperative antibiotics when indicated, short-term Foley catheter use, early ambulation, and DVT prophylaxis (eg, anticoagulation, compression stockings).
- Fevers before postoperative day 3 are unlikely to be infectious unless Clostridium or β-hemolytic streptococci are involved.

Shock

Defined as **inadequate tissue-level oxygenation to maintain vital organ function.** The multiple etiologies are differentiated by their cardiovascular effects and treatment options (see Table 2.17-4).

TABLE 2.17-3. Postoperative Fever Timing

Category	Time Frame	Etiology	Mnemonic
Immediate	Onset within hours.	Drug reaction, existing infection, malignant hyperthermia.	Wonder drugs
Acute	Onset within first week post-op.	Infection (wound, pneumonia, UTI, etc.).	Wind, water, wound
Subacute	Onset 1–4 weeks post-op.	Wound infection, line infection, DVT.	Walking
Delayed	Onset > 1 month.	Viral infection, indolent bacterial infections.	

MNEMONIC

The 6 W's of postoperative fever—

Wind: Atelectasis, pneumonia
Water: UTI
Wounds: Wound infection, abscess
Walking: DVT
Wonder drugs: Drug reaction
Womb: Endometritis

KEY FACT

Heart rate is the first vital sign to change in hemorrhagic shock. BP falls only after the loss of 30–40% of blood volume.

KEY FACT

Avoid pressors in hypovolemic shock until adequate fluid resuscitation has been provided.

KEY FACT

Malignant hyperthermia and neuroleptic malignant syndrome (NMS) should be ruled out in any suspected case of hyperthermia. Malignant hyperthermia would be seen after halothane exposure and NMS after a neuroleptic. Both conditions are treated with dantrolene.

KEY FACT

Following a bite, healthy domestic animals should be observed for 10 days. Skunks, raccoons, foxes, and bats should be euthanized and tested for rabies immediately.

Q

A 36-year-old woman is brought in by emergency medical services after suspected cocaine overdose. The patient is found to be in ventricular tachycardia and after cardioversion complains of abdominal pain. What study should be ordered?

TABLE 2.17-4. Types of Shock

Type	Major Causes	Cardiac Output	PCWP	PVR	Treatment
Hypovolemic	Trauma, blood loss, dehydration with inadequate fluid repletion, third spacing, burns.	↓	↓	↑	Replete with isotonic solution (eg, LR or NS) and blood in a 3:1 (fluid-to-blood) ratio. Initiate blood transfusion for continued blood loss.
Cardiogenic	CHF, arrhythmia, structural heart disease (severe mitral regurgitation, VSD), MI (> 40% of left ventricular function).	↓	↑	↑	Identify the cause and treat if possible. Give inotropic support with pressors such as dopamine (if hypotensive) or dobutamine (if not hypotensive).
Obstructive	Cardiac tamponade, tension pneumothorax, massive pulmonary embolism.	↓	↑	↑	Treat the underlying cause: Pericardiocentesis, decompression of pneumothorax, thrombolysis.
Distributive		↑	↓	↓	
Septic	Bacteremia, especially gram-⊖ organisms.				Administer broad-spectrum antibiotics. Measure central venous pressure (CVP) and give fluid until CVP = 8. Pressors (norepinephrine or dopamine) may be needed. Obtain cultures prior to the administration of antibiotics.
Anaphylactic	Bee sting, medications, food allergy.				1:1000 epinephrine. Consider adjuncts H_1/H_2 antagonists and steroids.
SIRS (systemic inflammatory response syndrome)	Pancreatitis, burns, trauma.				Manage underlying cause.
Neurogenic	Brain or spinal cord injury.				Maintain pressures with fluid and pressor support.

Thermal Dysregulation

HYPOTHERMIA

A body temperature < 35°C (< 95°F). May present with mental status and neurologic deficits.

Diagnosis

- Exposure: burns, infection (sepsis), trauma, drugs.
- Endocrine/metabolic: hypothyroidism, hypoadrenalism, hypoglycemia.
- Neurologic: spinal cord injury, CVA.

A

Cocaine use may lead to nonobstructive mesenteric ischemia as a result of perfusion deficits 2° to cardiac arrhythmias. Abdominal CT angiography should be ordered to screen for ischemia.

Management

- Remove the patient from the cold or windy environment and remove wet clothing. In mild cases, passively rewarm the patient with blankets or warm water. Also administer warm air and warm IV fluids.
- In more severe cases, the patient may need active rewarming with heating blankets, radiant heat, or warm water immersion. In unstable patients, active core rewarming may be necessary (eg, NG or bladder lavage, pleural lavage, or cardiac bypass). If the patient has frostbite, thaw the affected areas with the same methods. Patients will need narcotic analgesia for thawing.
- Monitor the ECG for arrhythmias such as bradycardia and slow AF, which can be common at < 30°C (< 86°F). The classic sign is the **J wave** (aka Osborn wave). Also monitor electrolytes and acid-base balance.
- Do not stop resuscitation efforts until the patient has been warmed.

HYPERTHERMIA

A body temperature > 40°C (> 104°F).

Diagnosis

- Exposure: Malignant hyperthermia, NMS, poisoning, overdose, withdrawal syndrome, environmental.
- Infectious: Sepsis, meningitis/encephalitis, tetanus, typhoid, malaria.
- Endocrine: Thyroid storm, pheochromocytoma, diabetic ketoacidosis.
- Neurologic: Hypothalamic stroke, seizures, CVA.
- Oncologic.

Management

Rapidly cool the patient with cold water, wet blankets, and ice. Give a benzodiazepine to prevent shivering. Rule out causes of fever such as infection or drug reaction.

Bites and Stings

Table 2.17-5 outlines the management of common bites and stings. Table 2.17-6 summarizes the recommended prophylaxis for rabies and tetanus.

Toxicology

CARBON MONOXIDE POISONING

A **hypoxemic poisoning syndrome** seen in patients who have been exposed to automobile exhaust, smoke inhalation, barbecues, or old appliances in poorly ventilated locations.

History/Pe

- Presents with hypoxemia, **cherry-red skin** (rare), confusion, and **headaches.** Coma or seizures occur in severe cases.
- Chronic low-level exposure may cause **flulike symptoms** with generalized myalgias, nausea, and headaches. Ask about symptoms in others living in the same house.

KEY FACT

In carbon monoxide poisoning, the measured O_2 saturation is usually normal. This is because the pulse oximeter recognizes carboxyhemoglobin as a normal saturated hemoglobin molecule, so it does not adequately reflect the low arterial Po_2 levels.

KEY FACT

Bites involving sharp teeth and resulting in deep puncture should not be sutured closed. Treat with antibiotics and monitor for developing deep tissue infections including osteomyelitis.

KEY FACT

Consider imaging cat bites for possible tooth fragments implanted in wound.

KEY FACT

Common microbiology of bites: Pasteurella species, Capnocytophaga canimorsus, Bartonella, as well as staphylococcus and streptococcus species.

Q

A 44-year-old woman is brought to the ED following a motor vehicle collision. On arrival, her BP is 70/35 mm Hg and her heart rate 110 bpm. Physical examination reveals bruises over the chest and abdomen. A pulmonary artery catheter is placed and reveals a PCWP of 16 mm Hg. After resuscitation with 2 L of crystalloid, BP and heart rate measurements are 80/40 mm Hg and 125 bpm. PCWP is now 24 mm Hg. What is the most likely diagnosis?

TABLE 2.17-5. Management of Bites and Stings

Source	Potential Complication	Management
Bees and wasps	Anaphylaxis.	Antihistamines and steroids; IM epinephrine if anaphylaxis develops.
Spiders	Necrosis, hypocalcemia.	Supportive measures; antivenom if available. Surgical resection and skin grafts for severe necrosis.
Scorpions	In severe cases, cranial nerve dysfunction, excessive motor activity, respiratory compromise.	Supportive with benzodiazepines and analgesics; atropine for hypersalivation and respiratory distress (not to be used with foreign scorpion stings); IV scorpion-specific antibody.
Snakes	Venom poisoning.	Antivenom is the mainstay of treatment. Keep the affected limb below the heart. Compression bands help, but tourniquets are contraindicated. Suction and incision are dangerous and should not be done.
Dogs and cats	Infection, rabies/tetanus.	Amoxicillin/clavulanate for puncture wounds, bites to hands/feet, and high-risk or immunocompromised patients.
Humans	Infection.	Amoxicillin/clavulanate unless very minor.
Rodents	Low risk of infection; not known to carry rabies.	Local wound care.

KEY FACT

Ipecac syrup is an antiquated treatment for poisoning that is rarely if ever used because of the risks of ↑ damage caused by emesis and the lack of demonstrated patient benefit.

- **Suspect smoke inhalation** in the presence of **singed nose hairs, facial burns, hoarseness, wheezing,** or **carbonaceous sputum.**

Diagnosis

- Check an ABG and serum carboxyhemoglobin level (normal is < 5% in nonsmokers and < 10% in smokers).
- Check an ECG in the elderly and in patients with a history of cardiac disease.

TABLE 2.17-6. Rabies and Tetanus Precautions

Suspected Pathogen	Exposure	Prophylaxis
Rabies	Bites from dogs, cats, ferrets, skunks, raccoons, **bats.**	If an animal displays signs of rabies, administer 1 dose of human rabies immune globulin and 4 doses of rabies vaccine over 14 days if the patient has never been vaccinated. Previously vaccinated patients do not need immune globulin and require only 2 doses of vaccine.
Tetanus	Any wound.	Administer tetanus toxoid if the patient had 3 or fewer lifetime toxoids or the last was 10 or more years ago for a minor/clean wound or 5 or more years ago for all other wounds. Administer tetanus immune globulin only if wound is major/dirty and the patient had 3 or fewer lifetime toxoids.

A

Cardiogenic or obstructive shock probably caused by severe blunt trauma to the chest. The patient has signs of shock, and her elevated PCWP suggests either a cardiogenic or an obstructive cause. On the basis of the mechanism of injury, she may have severe myocardial contusion or cardiac tamponade.

Treatment

- Treat with 100% O_2 until patient is asymptomatic and carboxyhemoglobin falls to normal.
- Use **hyperbaric O_2** for pregnant patients, nonresponders, those with signs of CNS or cardiac ischemia, or those with severely ↑ carboxyhemoglobin to facilitate displacement of carbon monoxide from hemoglobin.
- Patients with **airway burns** or **smoke inhalation** may require early intubation, as upper airway edema can rapidly lead to complete obstruction.

COMMON DRUG INTERACTIONS/REACTIONS

Table 2.17-7 outlines drug interactions and reactions that are commonly encountered.

DRUG OVERDOSE

Table 2.17-8 summarizes antidotes and treatments for substances commonly encountered in overdoses and intoxications. If a patient is unresponsive, it is common to empirically treat with a dose of naloxone.

MAJOR DRUG SIDE EFFECTS

Table 2.17-9 outlines the major side effects of select drugs.

KEY FACT

While activated charcoal is the preferred method of decontamination, orogastric lavage may be indicated for life-threatening toxins ≤ 1 hour after ingestion.

KEY FACT

Activated charcoal is indicated for cases of recent isolated ingestion (< 2 hours) of substances known to adsorb to it (not used for lithium, iron, lead, hydrocarbons, or toxic alcohols).

TABLE 2.17-7. Drug Interactions and Reactions

Interaction/Reaction	Drugs
Induction of P-450 enzymes	**Barb**iturates, **S**t. John's wort, **P**henytoin, **R**ifampin, **G**riseofulvin, **C**arbamazepine: "**Barb**ara **S**teals **P**hen-phen and **R**efuses **G**reasy **C**arbs."
Inhibition of P-450 enzymes	Quinidine, cimetidine, ketoconazole, INH, grapefruit, erythromycin, sulfonamides.
Metabolism by P-450 enzymes	Benzodiazepines, amide anesthetics, metoprolol, propranolol, nifedipine, phenytoin, quinidine, theophylline, warfarin, barbiturates.
↑ risk of digoxin toxicity	Quinidine, cimetidine, amiodarone, CCBs.
Competition for albumin-binding sites	Warfarin, ASA, phenytoin.
Blood dyscrasias	Ibuprofen, quinidine, methyldopa, chemotherapeutic agents.
Hemolysis in G6PD-deficie t patients	Sulfonamides, INH, ASA, ibuprofen, nitrofurantoin, primaquine, pyrimethamine, chloramphenicol.
Gynecomastia	**S**pironolactone, **E**strogens, **D**igitalis, **C**imetidine, chronic **A**lcohol use, **K**etoconazole: "**S**ome **E**xcellent **D**rugs **C**reate **A**wesome **K**nockers."
Stevens-Johnson syndrome	Anticonvulsants, sulfonamides, penicillins.
Photosensitivity	Tetracycline, amiodarone, sulfonamides.
Drug-induced SLE	Procainamide, hydralazine, INH, penicillamine, chlorpromazine, methyldopa, quinidine.

TABLE 2.17-8. Specific Antidotes

Toxin	Antidote/Treatment
Acetaminophen	N-acetylcysteine.
Acid/alkali ingestion	Upper endoscopy to evaluate for stricture.
Anticholinesterases, organophosphates	Atropine, pralidoxime.
Antimuscarinic/anticholinergic agents	Physostigmine.
Arsenic, mercury, gold	Succimer, dimercaprol.
β-blockers	Glucagon.
Barbiturates (phenobarbital)	Urine alkalinization, dialysis, activated charcoal, supportive care.
Benzodiazepines	Flumazenil (can precipitate withdrawal, mainly used for acute ingestion).
Black widow bite	Calcium gluconate, methocarbamol.
Carbon monoxide	100% O_2, hyperbaric O_2.
Copper, arsenic, lead, gold	Penicillamine.
Cyanide	Hydroxycobalamin, amyl nitrate, sodium nitrate, sodium thiosulfate.
Digitalis	Normalize K^+ but avoid giving Ca^{2+}, Mg^{2+}, or lidocaine (for torsades); anti-digitalis Fab.
Heparin	Protamine sulfate.
INH	Pyridoxine.
Iron salts	Deferoxamine.
Lead	Succimer, CaEDTA, dimercaprol.
Methanol, ethylene glycol (antifreeze)	EtOH, fomepizole, dialysis, calcium gluconate for ethylene glycol.
Methemoglobin	Methylene blue.
Opioids	Naloxone.
Salicylates	Urine alkalinization, dialysis, activated charcoal.
TCAs	Sodium bicarbonate for QRS prolongation; diazepam or lorazepam for seizures; cardiac monitor for arrhythmias.
Theophylline	Activated charcoal. Consider repeat doses.
tPA, streptokinase	Aminocaproic acid.
Warfarin	Vitamin K, FFP.

TABLE 2.17-9. Drug Side Effects

Drug	Side Effects
ACEIs	**Cough,** rash, proteinuria, angioedema, taste changes, teratogenic effects.
Amantadine	Ataxia, **livedo reticularis.**
Aminoglycosides	Ototoxicity, nephrotoxicity (acute tubular necrosis).
Amiodarone	Acute: AV block, hypotension, bradycardia. Chronic: pulmonary fibrosis, peripheral deposition leading to bluish discoloration, arrhythmias, hypo-/hyperthyroidism, corneal deposition.
Amphotericin	Fever/rigors, nephrotoxicity, bone marrow suppression, anemia.
Antipsychotics	Sedation, acute dystonic reaction, akathisia, parkinsonism, tardive dyskinesia, **NMS.**
Azoles (eg, fluconazole)	Inhibition of P-450 enzymes.
AZT	Thrombocytopenia, megaloblastic anemia.
β-blockers	Asthma exacerbation, masking of hypoglycemia, impotence, bradycardia, AV block, CHF.
Benzodiazepines	Sedation, dependence, respiratory depression.
Bile acid resins	GI upset, malabsorption of vitamins and medications.
Carbamazepine	Induction of P-450 enzymes, **agranulocytosis,** aplastic anemia, liver toxicity.
CCBs	Peripheral edema, constipation, cardiac depression.
Chloramphenicol	**Gray baby syndrome,** aplastic anemia.
Cisplatin	Nephrotoxicity, acoustic nerve damage.
Clonidine	Dry mouth; **severe rebound headache and hypertension.**
Clozapine	Agranulocytosis.
Corticosteroids	Mania, hyperglycemia (acute), immunosuppression, bone mineral loss, thinning of skin, easy bruising, myopathy, cataracts (chronic).
Cyclophosphamide	Myelosuppression, **hemorrhagic cystitis.**
Digoxin	GI disturbance, **yellow visual changes, arrhythmias** (eg, junctional tachycardia or SVT).
Doxorubicin	**Cardiotoxicity (cardiomyopathy).**
Ethyl alcohol	Acidosis, renal dysfunction, CNS depression.
Fluoroquinolones	Cartilage damage in children; Achilles tendon rupture in adults.
Furosemide	Ototoxicity, hypokalemia, nephritis, gout.

(continues)

TABLE 2.17-9. Drug Side Effects (continued)

Drug	Side effects
Gemfibrozil	Myositis, reversible ↑ in LFTs.
Halothane	Hepatotoxicity, **malignant hyperthermia.**
HCTZ	Hypokalemia, hyponatremia, hyperuricemia, hyperglycemia, hypercalcemia.
HMG-CoA reductase inhibitors	Myositis, reversible ↑ in LFTs.
Hydralazine	Drug-induced SLE.
Hydroxychloroquine	Retinopathy.
INH	Peripheral neuropathy **(prevent with pyridoxine/vitamin B_6),** hepatotoxicity, inhibition of P-450 enzymes, seizures with overdose, hemolysis in G6PD deficiency.
MAOIs	**Hypertensive tyramine reaction, serotonin syndrome** (with meperidine).
Methanol	Blindness, anion-gap metabolic acidosis.
Methotrexate	Hepatic fibrosis, pneumonitis, anemia.
Methyldopa	⊕ Coombs test, drug-induced SLE.
Metronidazole	Disulfiram reaction, vestibular dysfunction, **metallic taste.**
Niacin	**Cutaneous flushing.**
Nitroglycerin	Hypotension, tachycardia, headache, tolerance.
Penicillamine	Drug-induced SLE.
Penicillin/β-lactams	Hypersensitivity reactions.
Phenytoin	Nystagmus, diplopia, ataxia, arrhythmia (in toxic doses), **gingival hyperplasia,** hirsutism, teratogenic effects.
Prazosin	First-dose hypotension.
Procainamide	Drug-induced SLE.
Propylthiouracil	Agranulocytosis, aplastic anemia.
Quinidine	Cinchonism (headache, tinnitus), thrombocytopenia, arrhythmias (eg, **torsades de pointes**).
Reserpine	Depression.
Rifampin	Induction of P-450 enzymes; **orange-red body secretions.**
Salicylates	Fever; hyperventilation with **respiratory alkalosis and metabolic acidosis;** dehydration, diaphoresis, hemorrhagic gastritis.

(continues)

TABLE 2.17-9. Drug Side Effects (continued)

Drug	Side effects
SSRIs	Anxiety, **sexual dysfunction,** serotonin syndrome if taken with MAOIs.
Succinylcholine	**Malignant hyperthermia,** hyperkalemia.
TCAs	Sedation, coma, anticholinergic effects, seizures, **QRS prolongation,** arrhythmias.
Tetracyclines	Tooth discoloration, photosensitivity, Fanconi syndrome, GI distress.
Trimethoprim	Megaloblastic anemia, leukopenia, granulocytopenia.
Valproic acid	Teratogenicity leads to neural tube defects; rare fatal hepatotoxicity.
Vancomycin	Nephrotoxicity, ototoxicity, **"red man syndrome"** (histamine release; not an allergy).
Vinblastine	Severe myelosuppression.
Vincristine	Peripheral neuropathy, paralytic ileus.

MANAGEMENT OF DRUG WITHDRAWAL

Table 2.17-10 summarizes common drug withdrawal symptoms and treatment.

TABLE 2.17-10. Symptoms and Treatment of Drug Withdrawal

Drug	Withdrawal Symptoms	Treatment
Alcohol	Tremor (6–12 hours). Tachycardia, hypertension, agitation, seizures (within 48 hours). Hallucinations, **DTs**—severe autonomic instability leading to tachycardia, hypertension, delirium, and possibly death (within 2–7 days). Mortality is 15–20%.	**Benzodiazepines** (can require massive doses); haloperidol for hallucinations; **thiamine,** folate, and multivitamin replacement (do not affect withdrawal, but most alcoholics are deficient).
Barbiturates	Anxiety, seizures, delirium, tremor; tachycardia and hypertension.	**Benzodiazepines.**
Benzodiazepines	Rebound anxiety, seizures, tremor, insomnia.	**Benzodiazepine taper.**
Cocaine/ amphetamines	Depression, hyperphagia, hypersomnolence.	Supportive treatment. Avoid pure β-blockers (may lead to unopposed α activity, causing hypertension).
Opioids	Anxiety, insomnia, flulike symptoms, piloerection, fever, rhinorrhea, lacrimation, yawning, nausea, stomach cramps, diarrhea, mydriasis.	Antiemetics, muscle relaxers, and NSAIDs for mild symptoms; clonidine, buprenorphine, or methadone for moderate to severe symptoms.

RECOGNITION OF DRUG INTOXICATION

See the Psychiatry chapter for a summary of common drug intoxication symptoms.

Vitamin Deficiencie

Table 2.17-11 summarizes the signs and symptoms of key vitamin deficiencies.

TABLE 2.17-11. Vitamin Functions and Deficiencie

Vitamin	Signs/Symptoms of deficiency
Vitamin A	Night blindness, dry skin.
Vitamin B_1 (thiamine)	Beriberi (polyneuritis, dilated cardiomyopathy, high-output CHF, edema), Wernicke-Korsakoff syndrome.
Vitamin B_2 (riboflavin)	Angular stomatitis, cheilosis, corneal vascularization.
Vitamin B_3 (niacin)	Pellagra (diarrhea, dermatitis, dementia).
Vitamin B_5 (pantothenate)	Dermatitis, enteritis, alopecia, adrenal insufficiency.
Vitamin B_6 (pyridoxine)	Convulsions, hyperirritability; required during administration of INH.
Vitamin B_{12} (cobalamin)	Macrocytic, megaloblastic anemia; neurologic symptoms (eg, optic neuropathy, subacute combined degeneration, paresthesias); glossitis.
Vitamin C	Scurvy (eg, swollen gums, bruising, anemia, poor wound healing).
Vitamin D	Rickets in children (bending bones), osteomalacia in adults (soft bones), hypocalcemic tetany.
Vitamin E	↑ fragility of RBCs.
Vitamin K	Neonatal hemorrhage; ↑ PT and aPTT, normal BT.
Biotin	Dermatitis, enteritis. Can be caused by ingestion of **raw eggs** or antibiotic use.
Folic acid	The **most common vitamin deficiency in the United States.** Sprue; macrocytic, megaloblastic anemia without neurologic symptoms.
Magnesium	Weakness, muscle cramps, exacerbation of hypocalcemic tetany, CNS hyperirritability leading to tremors, choreoathetoid movement.
Selenium	Keshan disease (cardiomyopathy).

HIGH-YIELD FACTS IN

RAPID REVIEW

Cardiovascular	518	Neurology	531
Dermatology	520	Obstetrics	532
Endocrinology	521	Gynecology	533
Epidemiology	522	Pediatrics	534
Ethics	523	Psychiatry	536
Gastrointestinal	524	Pulmonary	537
Hematology/Oncology	526	Renal/Genitourinary	538
Infectious Disease	528	Selected Topics In Emergency Medicine	540
Musculoskeletal	530		

CARDIOVASCULAR

Classic ECG finding in atrial flutter.	"Sawtooth" P waves.
Definition of unstable angina.	Angina that is new or worsening with no ↑ in troponin level.
Antihypertensive for a diabetic patient with proteinuria.	Angiotensin-converting enzyme inhibitor.
Beck triad for cardiac tamponade.	Hypotension, distant heart sounds, and jugular venous distention (JVD).
Drugs that slow heart rate.	β-blockers, calcium channel blockers (CCBs), digoxin, amiodarone.
Hypercholesterolemia treatment that leads to flushing and pruritus.	Niacin.
Murmur—hypertrophic obstructive cardiomyopathy.	A systolic ejection murmur heard along the lateral sternal border that ↑ with ↓ preload (Valsalva maneuver).
Murmur—aortic insufficiency.	Austin Flint murmur, a diastolic, decrescendo, low-pitched, blowing murmur that is best heard sitting up; ↑ with ↑ afterload (handgrip maneuver).
Murmur—aortic stenosis.	A systolic crescendo/decrescendo murmur that radiates to the neck; ↑ with ↑ preload (squatting maneuver).
Murmur—mitral regurgitation.	A holosystolic murmur that radiates to the axilla; ↑ with ↑ afterload (handgrip maneuver).
Murmur—mitral stenosis.	A diastolic, mid- to late, low-pitched murmur preceded by an opening snap.
Treatment for atrial fibrillation and atrial flutter.	If unstable, cardiovert. If stable or chronic, rate control with CCBs or β-blockers.
Treatment for ventricular fibrillation.	Immediate cardioversion.
Dressler syndrome.	An autoimmune reaction with fever, pericarditis, and ↑ ESR occurring 2–4 weeks post-MI.
IV drug use with JVD and a holosystolic murmur at the left sternal border. Treatment?	Treat existing heart failure, and replace the tricuspid valve.
Diagnostic test for hypertrophic cardiomyopathy.	Echocardiogram (showing a thickened left ventricular wall and outflow obstruction).
Pulsus paradoxus.	A ↓ in systolic BP of > 10 mm Hg with inspiration; seen in cardiac tamponade.
Classic ECG findings in pericarditis.	Low-voltage, diffuse S-segment elevation.
Eight surgically correctable causes of hypertension.	Renal artery stenosis, coarctation of the aorta, pheochromocytoma, Conn syndrome, Cushing syndrome, unilateral renal parenchymal disease, hyperthyroidism, hyperparathyroidism.

Evaluation of a pulsatile abdominal mass and bruit.	Abdominal ultrasound and CT.
Indications for surgical repair of abdominal aortic aneurysm.	> 5.5 cm, rapidly enlarging, symptomatic, or ruptured.
Treatment for acute coronary syndrome.	ASA, heparin, clopidogrel, morphine, O_2, sublingual nitroglycerin, IV β-blockers.
Metabolic syndrome.	Abdominal obesity, high triglycerides, low HDL, hypertension, insulin resistance, prothrombotic or proinflamm tory states.
Appropriate diagnostic test? ■ A 50-year-old man with stable angina can exercise to 85% of maximum predicted heart rate. ■ A 65-year-old woman with left bundle branch block and severe osteoarthritis has unstable angina.	Exercise stress treadmill with ECG. Pharmacologic stress test (eg, dobutamine echo).
Signs of active ischemia during stress testing.	Angina, ST-segment changes on ECG, or ↓ BP.
ECG findings suggesting MI	ST-segment elevation (depression means ischemia), fl ttened T waves, and Q waves.
Coronary territories in MI.	Anterior wall (LAD/diagonal), inferior (PDA), posterior (left circumfl x/oblique, RCA/marginal), septum (LAD/diagonal).
A young patient with angina at rest and ST-segment elevation with normal cardiac enzymes.	Prinzmetal angina.
Common symptoms associated with silent MIs.	CHF, shock, and altered mental status.
Diagnostic test for pulmonary embolism.	Spiral CT with contrast.
Protamine.	Reverses the ef ects of heparin.
Prothrombin time.	The coagulation parameter af ected by warfarin.
A young patient with a family history of sudden death collapses and dies while exercising.	Hypertrophic cardiomyopathy.
Endocarditis prophylaxis regimens.	Oral surgery—amoxicillin for certain situations; GI or GU procedures—not recommended.
Virchow triad.	Stasis, hypercoagulability, endothelial damage.
The most common cause of hypertension in young women.	OCPs.
The most common cause of hypertension in young men.	Excessive EtOH.
Figure 3 sign.	Aortic coarctation.
Water bottle–shaped heart.	Pericardial effusion. ook for pulsus paradoxus.

DERMATOLOGY

"Stuck-on" waxy appearance.	Seborrheic keratosis.
Red plaques with silvery-white scales and sharp margins.	Psoriasis.
The most common type of skin cancer; the lesion is a pearly-colored papule with a translucent surface and telangiectasias.	Basal cell carcinoma.
Honey-crusted lesions.	Impetigo.
A febrile patient with a history of diabetes presents with a red, swollen, painful lower extremity.	Cellulitis.
⊕ Nikolsky sign.	Pemphigus vulgaris.
⊖ Nikolsky sign.	Bullous pemphigoid.
A 55-year-old obese patient presents with dirty, velvety patches on the back of the neck.	Acanthosis nigricans. Check fasting blood glucose to rule out diabetes.
Dermatomal distribution.	Varicella zoster.
Flat-topped papules.	Lichen planus.
Irislike target lesions.	Erythema multiforme.
A lesion occurring in a geometric pattern in areas where skin comes into contact with clothing or jewelry.	Contact dermatitis.
Presents with one large patch and many smaller ones in a treelike distribution.	Pityriasis rosea.
Flat, often hypopigmented lesions on the chest and back; KOH prep has a "spaghetti-and-meatballs" appearance.	Tinea (pityriasis) versicolor.
Five characteristics of a nevus suggestive of melanoma.	Asymmetry, border irregularity, color variation, large diameter, changing appearance.
A premalignant lesion from sun exposure that can lead to squamous cell carcinoma.	Actinic keratosis.
Crusting vesicles in all stages of evolution on entire body.	Lesions of 1° varicella.
"Cradle cap."	Seborrheic dermatitis. Treat conservatively with bathing and moisturizing agents.
Associated with Propionibacterium acnes and changes in androgen levels, and the treatment of last resort.	Acne vulgaris. Last-resort treatment is oral isotretinoin (requires monthly blood tests).
A painful, recurrent vesicular eruption of mucocutaneous surfaces.	Herpes simplex.

Inflamm tion and epithelial thinning of the anogenital area, predominantly in postmenopausal women.	Lichen sclerosus.
Exophytic nodules on the skin with scaling or ulceration; the second most common type of skin cancer.	Squamous cell carcinoma.

ENDOCRINOLOGY

The most common cause of hypothyroidism.	Hashimoto thyroiditis.
Lab findings in Hashimo o thyroiditis.	High TSH, low T_4, antibodies to thyroid peroxidase (TPO).
Exophthalmos, pretibial myxedema, and ↓ TSH.	Graves disease.
The most common cause of Cushing syndrome.	Iatrogenic corticosteroid administration. The second most common cause is Cushing disease.
A patient post-thyroidectomy presents with signs of hypocalcemia and ↑ phosphorus.	Hypoparathyroidism (iatrogenic).
"Stones, bones, groans, psychiatric overtones."	Signs and symptoms of hypercalcemia.
Hypertension, hypokalemia, and metabolic alkalosis.	1° hyperaldosteronism (due to Conn syndrome or bilateral adrenal hyperplasia).
A patient presents with tachycardia, wild swings in BP, headache, diaphoresis, altered mental status, and a sense of panic.	Pheochromocytoma.
Which should be used first in t eating pheochromocytoma, α- or β-antagonists?	α-antagonists (phenoxybenzamine).
A patient with a history of lithium use presents with copious amounts of dilute urine.	Nephrogenic diabetes insipidus (DI).
Treatment of central DI.	Administration of DDAVP and free-water restriction.
A postoperative patient with significa t pain presents with hyponatremia and normal volume status.	Syndrome of inappropriate antidiuretic hormone (SIADH) due to stress.
An antidiabetic agent associated with lactic acidosis.	Metformin.
A patient presents with weakness, nausea, vomiting, weight loss, and new skin pigmentation. Lab results show hyponatremia and hyperkalemia. Treatment?	1° adrenal insufficie y (Addison disease). Treat with glucocorticoids, mineralocorticoids, and IV fluid .
Goal HbA_{1c} for a patient with diabetes mellitus (DM).	< 7.0%.
Treatment of diabetic ketoacidosis (DKA).	Fluids, insulin, and electrolyte repletion (eg, K^+).
Bone pain, hearing loss, ↑ alkaline phosphatase.	Paget disease.
↑ IGF-1.	Acromegaly.

Galactorrhea, amenorrhea, bitemporal hemianopia.	Prolactinoma.
↑ serum 17-hydroxyprogesterone.	Congenital adrenal hyperplasia (21-hydroxylase deficien y).
Pancreas, pituitary, parathyroid tumors.	Multiple endocrine neoplasia type 1 (MEN 1).

EPIDEMIOLOGY

How do you interpret the following 95% confiden e interval (CI) for a relative risk (RR) of 0.582: 95% CI 0.502, 0.673?	These data are consistent with RRs ranging from 0.502 to 0.673 with 95% confiden e (ie, we are confide t that, 95 out of 100 times, the true RR will be between 0.502 and 0.673).
Bias introduced into a study when a clinician is aware of the patient's treatment type.	Observational bias.
Bias introduced when screening detects a disease earlier and thus lengthens the time from diagnosis to death, but does not improve survival.	Lead-time bias.
If you want to know if geographic location af ects infant mortality rate but most variation in infant mortality is predicted by socioeconomic status, then socioeconomic status is a _____.	Confounding variable.
The proportion of people who have the disease and test ⊕ is the _____.	Sensitivity.
Sensitive tests have few false ⊖s and are used to rule _____ a disease.	Out.
PPD reactivity is used as a screening test because most people with TB (except those who are anergic) will have a ⊕ PPD. Highly sensitive or specific	Highly sensitive for TB. Screening tests with high sensitivity are good for diseases with low prevalence.
Chronic diseases such as systemic lupus erythematosus—higher prevalence or incidence?	Higher prevalence.
Epidemics such as influenza—higher p evalence or incidence?	Higher incidence.
What is the dif erence between incidence and prevalence?	Prevalence is the percentage of cases of disease in a population at one point in time. Incidence is the percentage of new cases of disease that develop over a given time period among the total population at risk. (Prevalence = Incidence × Duration)
Cross-sectional survey—incidence or prevalence?	Prevalence.
Cohort study—incidence or prevalence?	Incidence and prevalence.
Case-control study—incidence or prevalence?	Neither.
Describe a test that consistently gives identical results, but the results are wrong.	High reliability (precision), low validity (accuracy).

Dif erence between a cohort and a case-control study.	Cohort divides groups by an exposure and looks for development of disease. Case-control divides groups by a disease and assigns controls, and then goes back and looks for exposures.
Attributable risk?	The dif erence in risk in the exposed and unexposed groups (ie, the risk that is attributable to the exposure).
Relative risk?	Incidence in the exposed group divided by the incidence in the nonexposed group.
The results of a hypothetical study found an association between ASA intake and risk of heart disease. How do you interpret an RR of 1.5?	In patients who took ASA, the risk of heart disease was 1.5 times that of patients who did not take ASA.
Odds ratio?	In cohort studies, the odds of developing the disease in the exposed group divided by the odds of developing the disease in the nonexposed group. In case-control studies, the odds that the cases were exposed divided by the odds that the controls were exposed. In cross-sectional studies, the odds that the exposed group has the disease divided by the odds that the nonexposed group has the disease.
The most common cancer in men and the most common cause of death from cancer in men.	Prostate cancer is the most common cancer in men, but lung cancer causes more deaths.
The percentage of cases within 1 standard deviation (SD) of the mean? 2 SDs? 3 SDs?	68%, 95.4%, 99.7%.
Birth rate?	Number of live births per 1000 population in 1 year.
Mortality rate?	Number of deaths per 1000 population in 1 year.
Neonatal mortality rate?	Number of deaths from birth to 28 days per 1000 live births in 1 year.
Infant mortality rate?	Number of deaths from birth to 1 year of age per 1000 live births (neonatal + postnatal mortality) in 1 year.
Maternal mortality rate?	Number of deaths during pregnancy to 90 days postpartum per 100,000 live births in 1 year.

ETHICS

True or false: Once patients sign a statement giving consent, they must continue treatment.	False. Patients may change their minds at any time. Exceptions to the requirement of informed consent include emergency situations and patients without decision-making capacity.
A 15-year-old pregnant girl requires hospitalization for preeclampsia. Is parental consent required?	No. Parental consent is not necessary for the medical treatment of pregnant minors.
A doctor refers a patient for an MRI at a facility he/she owns.	Confli t of interest.

Involuntary psychiatric hospitalization can be undertaken for which three reasons?	The patient is a danger to self, a danger to others, or gravely disabled (unable to provide for basic needs).
True or false: It is more difficult to justify the withdrawal of care than to have withheld the treatment in the first place.	False. Withdrawing nonbeneficial treatment or treatment a patient no longer wants is ethically equivalent to withholding care.
A mother refuses to allow her child to be vaccinated.	A parent has the right to refuse treatment for his/her child as long as it does not pose a serious threat to the well-being of the child.
When can a physician refuse to continue treating a patient on the grounds of futility?	When there is no rationale for treatment, maximal intervention is failing, a given intervention has already failed, and treatment will not achieve the goals of care.
An 8-year-old child is in a serious accident. She requires emergent transfusion, but her parents are not present.	Treat immediately. Consent is implied in emergency situations.
A 15-year-old girl seeking treatment for an STD asks that her parents not be told about her condition.	Minors may consent to care for STDs without parental consent or knowledge.
Conditions in which confidentiality must be overridden.	Real threat of harm to third parties; suicidal intentions; certain contagious diseases; elder and child abuse.
Involuntary commitment or isolation for medical treatment may be undertaken for what reason?	When treatment noncompliance represents a serious danger to public health (eg, active TB).
A 10-year-old child presents in status epilepticus, but her parents refuse treatment on religious grounds.	Treat because the disease represents an immediate threat to the child's life. Then seek a court order.
A son asks that his mother not be told about her recently discovered cancer.	A physician can withhold information from the patient only in the rare case of therapeutic privilege or if the patient requests not to be told.

GASTROINTESTINAL

A patient presents with sudden onset of severe, diffuse abdominal pain. Examination reveals peritoneal signs, and abdominal radiograph reveals free air under the diaphragm. Management?	Emergent laparotomy to repair a perforated viscus.
The most likely cause of acute lower GI bleeding in patients > 40 years of age.	Diverticulosis.
Diagnostic modality used when ultrasonography is equivocal for cholecystitis.	Hepatobiliary iminodiacetic acid (HIDA) scan.
Risk factors for cholelithiasis.	Fat, female, fertile, forty, flatulent.
Inspiratory arrest during palpation of the RUQ.	Murphy sign, seen in acute cholecystitis.
The most common cause of small-bowel obstruction (SBO) in patients with no history of abdominal surgery.	Hernia.

The most common cause of SBO in patients with a history of abdominal surgery.	Adhesions.
Identify key organisms causing diarrhea: ■ Most common bacterial organism. ■ Recent antibiotic use. ■ Camping. ■ Traveler's diarrhea. ■ Church picnics/mayonnaise. ■ Uncooked hamburgers. ■ Fried rice. ■ Poultry/eggs. ■ Raw seafood. ■ AIDS. ■ Pseudoappendicitis.	 Campylobacter. Clostridium difficile. Giardia. Enterotoxigenic Escherichia coli (ETEC). S aureus. Ecoli O157:H7. Bacillus cereus. Salmonella. Vibrio, hepatitis A virus (HAV). Isospora, Cryptosporidium, Mycobacterium avium complex (MAC). Yersinia, Campylobacter.
A 25-year-old Jewish man presents with pain and watery diarrhea after meals. Examination shows fistulas between the bowel and skin and nodular lesions on his tibias.	Crohn disease.
Inflammatory disease of the colon with an ↑ risk of colon cancer.	Ulcerative colitis (greater risk than Crohn).
Extraintestinal manifestations of IBD.	Uveitis, ankylosing spondylitis, pyoderma gangrenosum, erythema nodosum, 1° sclerosing cholangitis.
Medical treatment for IBD.	5-ASA agents and steroids during acute exacerbations.
A 30-year-old man with ulcerative colitis presents with fatigue, jaundice, and pruritus.	Primary sclerosing cholangitis.
Difference between Mallory-Weiss and Boerhaave tears.	Mallory-Weiss—superficial tear in the esophageal mucosa; Boerhaave—full-thickness esophageal rupture.
Charcot triad.	RUQ pain, jaundice, and fever/chills.
Reynolds pentad.	Charcot triad plus shock and mental status changes.
Medical treatment for hepatic encephalopathy.	↓ protein intake, lactulose, rifaximin.
The first step in the management of a patient with an acute GI bleeding episode.	Manage ABCs.
A 4-year-old child presents with oliguria, petechiae, and jaundice following an illness with bloody diarrhea. Most likely diagnosis and cause?	Hemolytic-uremic syndrome (HUS) due to Ecoli O157:H7.
Treatment after exposure to hepatitis B virus (HBV).	HBV immunoglobulin.
Classic causes of drug-induced hepatitis.	TB medications (INH, rifampin, pyrazinamide), acetaminophen, and tetracycline.
A 40-year-old obese woman with elevated alkaline phosphatase, elevated bilirubin, pruritus, dark urine, and clay-colored stools.	Biliary tract obstruction.

Hernia with highest risk of incarceration—indirect, direct, or femoral?	Femoral hernia.
Severe abdominal pain out of proportion to the examination.	Mesenteric ischemia.
Diagnosis of ileus.	Abdominal radiographs (could also perform CT scan).
A 50-year-old man with a history of alcohol abuse presents with boring epigastric pain that radiates to the back and is relieved by sitting forward. Management?	Confirm the diagnosis of acute pancreatitis with ↑ amylase and lipase. Make the patient NPO and give IV fluid, O_2, analgesia, and "tincture of time."
Colon cancer region based on symptoms: Anemia from chronic disease, occult blood loss, vague abdominal pain. Obstructive symptoms, change in bowel movements.	 Right sided: rare to have an obstruction. Left-sided: "apple–core" lesion.
Presents with watery diarrhea, dehydration, muscle weakness, and flushing.	VIPoma (replace fluids and electrolytes, may need to surgically resect tumor, or use octreotide).
Presents with palpable, nontender gallbladder.	Courvoisier sign (suggests pancreatic cancer).

HEMATOLOGY/ONCOLOGY

Four causes of microcytic anemia.	**TICS**–**T**halassemia, **I**ron deficiency, anemia of **C**hronic disease, and **S**ideroblastic anemia.
An elderly man with hypochromic, microcytic anemia is asymptomatic. Diagnostic tests?	Fecal occult blood test and sigmoidoscopy; suspect colorectal cancer.
Precipitants of hemolytic crisis in patients with G6PD deficiency.	Sulfonamides, antimalarial drugs, fava beans.
The most common inherited cause of hypercoagulability.	Factor V Leiden mutation.
The most common inherited bleeding disorder.	von Willebrand disease.
The most common inherited hemolytic anemia.	Hereditary spherocytosis.
Diagnostic test for hereditary spherocytosis.	Osmotic fragility test.
Pure RBC aplasia.	Diamond-Blackfan anemia.
Anemia associated with absent radii and thumbs, diffuse hyperpigmentation, café au lait spots, microcephaly, and pancytopenia.	Fanconi anemia.
Medications and viruses that lead to aplastic anemia.	Chloramphenicol, sulfonamides, radiation, HIV, chemotherapeutic agents, hepatitis, parvovirus B19, EBV.
How to distinguish polycythemia vera from 2° polycythemia.	Both have ↑ hematocrit and RBC mass, but polycythemia vera should have normal O_2 saturation and low erythropoietin levels.
Thrombotic thrombocytopenic purpura (TTP) pentad?	**"FAT RN": F**ever, **A**nemia, **T**hrombocytopenia, **R**enal dysfunction, **N**eurologic abnormalities.

Hemolytic uremic syndrome (HUS) triad?	Anemia, thrombocytopenia, and acute renal failure.
Treatment for TTP.	Emergent large-volume plasmapheresis, corticosteroids, antiplatelet drugs. Platelet transfusion is contraindicated!
Treatment for idiopathic thrombocytopenic purpura (ITP) in children.	Usually resolves spontaneously; may require IVIG and/or corticosteroids.
Which of the following are ↑ in DIC: fibrin split products, d-dimer, fibrinogen, platelets, and hematocrit?	Fibrin split products and d-dimer are ↑; platelets, fibrinogen, and hematocrit are ↓.
An 8-year-old boy presents with hemarthrosis and ↑ PTT with normal PT and bleeding time. Diagnosis? Treatment?	Hemophilia A or B; consider desmopressin (for hemophilia A) or factor VIII or IX supplements.
A 14-year-old girl presents with prolonged bleeding after dental surgery and with menses, normal PT, normal or ↑ PTT, and ↑ bleeding time. Diagnosis? Treatment?	von Willebrand disease; treat with desmopressin, FFP, or cryoprecipitate.
A 60-year-old African American man presents with bone pain. What might a workup for multiple myeloma reveal?	Monoclonal gammopathy, Bence Jones proteinuria, and "punched-out" lesions on radiographs of the skull and long bones.
Reed-Sternberg cells.	Hodgkin lymphoma.
A 10-year-old boy presents with fever, weight loss, and night sweats. Examination shows an anterior mediastinal mass. Suspected diagnosis?	Non-Hodgkin lymphoma.
Microcytic anemia with ↓ serum iron, ↓ total iron-binding capacity (TIBC), and normal or ↑ ferritin.	Anemia of chronic disease.
Microcytic anemia with ↓ serum iron, ↓ ferritin, and ↑ TIBC.	Iron-deficiency anemia.
An 80-year-old man presents with fatigue, lymphadenopathy, splenomegaly, and isolated lymphocytosis. What is the suspected diagnosis?	Chronic lymphocytic leukemia (CLL).
Patient with fatigue is found to have a ↓ hemoglobin and ↑ mean corpuscular volume. What are potential causes for this anemia?	↓ B_{12} (pernicious anemia, vegetarian diet, Crohn/GI disorders) or folate (alcoholics).
A late, life-threatening complication of chronic myelogenous leukemia (CML).	Blast crisis (fever, bone pain, splenomegaly, pancytopenia).
Auer rods on blood smear.	Acute myelogenous leukemia (AML).
AML subtype associated with DIC. Treatment?	M3. Retinoic acid.
Electrolyte changes in tumor lysis syndrome.	↓ Ca^{2+}, ↑ K^{+}, ↑ phosphate, ↑ uric acid.
A 50-year-old man presents with early satiety, splenomegaly, and bleeding. Cytogenetics show t(9,22). Diagnosis?	CML.
A patient on the chemotherapy service with an absolute neutrophil count (ANC) of 1000 is noted to have a fever of 38.8°C (102.1°F). Next best step?	Neutropenic fever is a medical emergency. Start broad-spectrum antibiotics.

Virus associated with aplastic anemia in patients with sickle cell anemia.	Parvovirus B19.
A 25-year-old African American man with sickle cell anemia has sudden onset of bone pain. Management of pain crisis?	O_2, analgesia, hydration, and, if severe, transfusion.
A significa t cause of morbidity in thalassemia patients. Treatment?	Iron overload; use deferoxamine.

INFECTIOUS DISEASE

The three most common causes of fever of unknown origin (FUO).	Infection, cancer, and autoimmune disease.
Four signs and symptoms of streptococcal pharyngitis.	Fever, tender anterior cervical lymphadenopathy, tonsillar exudate, lack of cough.
A nonsuppurative complication of streptococcal infection that is not altered by treatment of 1° infection.	Postinfectious glomerulonephritis.
The most common predisposing factor for acute sinusitis.	Viral URI.
Asplenic patients are particularly susceptible to these organisms.	Encapsulated organisms—pneumococcus, meningococcus, Haemophilus influenza , Klebsiella.
The number of bacteria needed on a clean-catch specimen to diagnose a UTI.	10^5 bacteria/mL.
Which healthy population is susceptible to UTIs?	Pregnant women. Treat this group aggressively because of high risk of complications.
A patient from California or Arizona presents with fever, malaise, cough, and night sweats. Diagnosis? Treatment?	Coccidioidomycosis; amphotericin B.
Nonpainful chancre.	1° syphilis.
A "blueberry muffin" rash is characteristic of what congenital infection?	Rubella.
Meningitis in neonates. Causes? Treatment?	Group B strep (GBS), Ecoli, Listeria. Treat with gentamicin and ampicillin.
Meningitis in infants. Causes? Treatment?	Pneumococcus, meningococcus, H influenza . Treat with cefotaxime and vancomycin.
What should always be done prior to LP?	Check for ↑ ICP; look for papilledema.
CSF findings	
▪ Low glucose, PMN predominance.	Bacterial meningitis.
▪ Normal glucose, lymphocytic predominance.	Aseptic (viral) meningitis.
▪ Numerous RBCs in serial CSF samples.	Subarachnoid hemorrhage (SAH).
▪ ↑ gamma globulins.	MS.

Initially presents with a pruritic papule with regional lymphadenopathy; evolves into a black eschar after 7–10 days. Treatment?	Cutaneous anthrax. Treat with penicillin G or ciprofl xacin.
Findings in 3° syphilis.	Tabes dorsalis, general paresis, gummas, Argyll Robertson pupil, aortitis, aortic root aneurysms.
Characteristics of 2° Lyme disease.	Arthralgias, migratory polyarthropathies, Bell palsy, myocarditis.
Cold agglutinins.	Mycoplasma.
A 24-year-old man presents with soft white plaques on his tongue and the back of his throat. Diagnosis? Workup? Treatment?	Candidal thrush. Workup should include an HIV test. Treat with nystatin oral suspension.
At what CD4 count should Pneumocystis jiroveci pneumonia prophylaxis be initiated in an HIV-⊕ patient? Mycobacterium avium–complex (MAC) prophylaxis?	≤ 200 for P jiroveci (with TMP-SMX); ≤ 50–100 for MAC (with clarithromycin/azithromycin).
Risk factors for pyelonephritis.	Pregnancy, vesicoureteral reflux, an tomic anomalies, indwelling catheters, kidney stones.
Neutropenic nadir postchemotherapy.	7–10 days.
Erythema migrans.	Lesion of 1° Lyme disease.
Classic physical findings or endocarditis.	Fever, heart murmur, Osler nodes, splinter hemorrhages, Janeway lesions, Roth spots.
Aplastic crisis in sickle cell disease.	Parvovirus B19.
Name the organism:	
▪ Branching rods in oral infection	Actinomyces israelii
▪ Weakly gram-⊕, partially acid-fast in lung infection	Nocardia asteroides
▪ Painful chancroid	Haemophilus ducreyi
▪ Dog or cat bite	Pasteurella multocida
▪ Gardener	Sporothrix schenckii
▪ Raw pork and skeletal muscle cysts	Trichinella spiralis
▪ Sheepherders with liver cysts	Echinococcus granulosus
▪ Perianal itching	Enterobius vermicularis
▪ Pregnant women with pets	Toxoplasma gondii
▪ Meningitis in adults	Neisseria meningitidis
▪ Meningitis in elderly	Streptococcus pneumoniae
▪ Meningoencephalitis in AIDS patients	Cryptococcus neoformans
▪ Alcoholic with pneumonia	Klebsiella
▪ "Currant jelly" sputum	Klebsiella
▪ Malignant external otitis	Pseudomonas
▪ Infection in burn victims	Pseudomonas
▪ Osteomyelitis from a foot wound puncture	Pseudomonas
▪ Osteomyelitis in a sickle cell patient	Salmonella

A 55-year-old man who is a smoker and a heavy drinker presents with a new cough and flulike symp oms. Gram stain shows no organisms; silver stain of sputum shows gram-⊖ rods. What is the diagnosis?	Legionella pneumonia.
A middle-aged man presents with acute-onset monoarticular joint pain and bilateral Bell palsy. What is the likely diagnosis, and how did he get it? Treatment?	Lyme disease, Ixodes tick, doxycycline.
A patient develops endocarditis 3 weeks after receiving a prosthetic heart valve. What organism is suspected?	S aureus or Staphylococcus epidermidis.
A patient develops endocarditis in a native valve after having a dental cleaning.	Streptococcus viridans.

MUSCULOSKELETAL

Back pain that is exacerbated by standing and walking and relieved with sitting and hyperfl xion of the hips.	Spinal stenosis.
Joints in the hand af ected in rheumatoid arthritis.	MCP and PIP joints; DIP joints are spared.
Joint pain and stiffness th t worsen over the course of the day and are relieved by rest.	Osteoarthritis.
A genetic disorder that is associated with multiple fractures and blue sclerae and is commonly mistaken for child abuse.	Osteogenesis imperfecta.
Hip and back pain along with stiffness th t improves with activity over the course of the day and worsens at rest. Diagnostic test?	Suspect ankylosing spondylitis. Check HLA-B27.
Arthritis, conjunctivitis, and urethritis in young men. Associated organisms?	Reactive (Reiter) arthritis. Most commonly associated with Chlamydia. Also consider Campylobacter, Shigella, Salmonella, and Ureaplasma.
A 55-year-old man has sudden, excruciating first TP joint pain after a night of drinking red wine. Diagnosis, workup, and chronic treatment?	Gout. Needle-shaped, negatively birefringent crystals are seen on joint fluid aspi ate. Chronic treatment with allopurinol or probenecid.
Rhomboid-shaped, positively birefringent crystals on joint fluid aspirate.	Pseudogout.
An elderly woman presents with pain and stiffness of the shoulders and hips; she cannot lift her arms above her head. Labs show anemia and ↑ ESR.	Polymyalgia rheumatica.
Bone is fractured in a fall on an outstretched hand.	Distal radius (Colles fracture).
A complication of scaphoid fracture.	Avascular necrosis.
Signs suggesting radial nerve damage with humeral fracture.	Wrist drop, loss of thumb abduction.
The most common 1° malignant tumor of bone.	Multiple myeloma.

Headaches, soreness in jaw, pain on scalp, transient monocular blindness?	Giant cell arteritis.

NEUROLOGY

Unilateral, severe periorbital headache with tearing and conjunctival erythema.	Cluster headache.
Prophylactic treatment for migraine.	Antihypertensives, antidepressants, anticonvulsants, dietary changes.
The most common pituitary tumor. Treatment?	Prolactinoma. Dopamine agonists (eg, bromocriptine).
A 55-year-old patient presents with acute "broken speech." What type of aphasia? What lobe and vascular distribution?	Broca aphasia. Frontal lobe, left MCA distribution.
The most common cause of subarachnoid hemorrhage (SAH).	Trauma; the second most common is berry aneurysm.
A crescent-shaped hyperdensity on CT that does not cross the midline.	Subdural hematoma—bridging veins torn.
A history significant for initial altered mental status with an intervening lucid interval. Diagnosis? Most likely source? Treatment?	Epidural hematoma. Middle meningeal artery. Neurosurgical evacuation.
CSF findings with SAH	↑ ICP, RBCs, xanthochromia.
Albuminocytologic dissociation.	Guillain-Barré syndrome (↑ protein in CSF without a significant ↑ in cell count).
Cold water is flushed into a patient's ear, and the fast phase of the nystagmus is toward the opposite side. Normal or pathologic?	Normal.
The most common 1° sources of metastases to the brain.	Lung, breast, skin (melanoma), kidney, GI tract.
May be seen in children who are accused of inattention in class and are often confused with ADHD.	Absence seizures.
The most frequent presentation of intracranial neoplasm.	Headache. 1° neoplasms are much less common than brain metastases.
The most common cause of seizures in children (2–10 years).	Infection, febrile seizures, trauma, idiopathic.
The most common cause of seizures in young adults (18–35 years).	Trauma, alcohol withdrawal, brain tumor.
First-line medication for status epilepticus.	IV benzodiazepine.
Confusion, ophthalmoplegia, ataxia.	Wernicke encephalopathy due to a deficiency of thiamine.
What % lesion in a symptomatic patient is an indication for carotid endarterectomy?	Seventy percent.
The most common causes of dementia.	Alzheimer disease and vascular/multi-infarct.

A combined upper motor neuron (UMN) and lower motor neuron (LMN) disorder.	Amyotrophic lateral sclerosis (ALS).
Rigidity and stiffness with unil teral resting tremor and masked facies.	Parkinson disease.
The mainstay of Parkinson therapy.	Levodopa/carbidopa.
Treatment for Guillain-Barré syndrome.	IVIG or plasmapheresis. Avoid steroids.
Rigidity and stiffness th t progress to choreiform movements, accompanied by moodiness and altered behavior.	Huntington disease.
A 6-year-old girl presents with a port-wine stain in the V_1 distribution as well as with intellectual disability, seizures, and ipsilateral leptomeningeal angioma.	Sturge-Weber syndrome. Treat symptomatically. Possible focal cerebral resection of the af ected lobe.
Multiple café au lait spots on skin.	Neurofib omatosis type 1.
Hyperphagia, hypersexuality, hyperorality, and hyperdocility.	Klüver-Bucy syndrome (amygdala).
May be administered to a symptomatic patient to diagnose myasthenia gravis.	Edrophonium.

OBSTETRICS

1° causes of third-trimester bleeding.	Placental abruption and placenta previa.
Classic ultrasonography and gross appearance of complete hydatidiform mole.	Snowstorm on ultrasonography. "Cluster-of-grapes" appearance on gross examination.
Chromosomal pattern of a complete mole.	46,XX.
Molar pregnancy containing fetal tissue.	Partial mole.
Symptoms of placental abruption.	Continuous, painful vaginal bleeding.
Symptoms of placenta previa.	Self-limited, painless vaginal bleeding.
When should a vaginal exam be performed with suspected placenta previa?	Never.
Antibiotics with teratogenic ef ects.	Tetracycline, fluo oquinolones, aminoglycosides, sulfonamides.
Medication given to accelerate fetal lung maturity.	Betamethasone or dexamethasone × 48 hours.
The most common cause of postpartum hemorrhage.	Uterine atony.
Treatment for postpartum hemorrhage.	Uterine massage; if that fails, give oxytocin.
Typical antibiotics for group B streptococcus (GBS) prophylaxis.	IV penicillin or ampicillin.

A patient fails to lactate after an emergency C-section with marked blood loss.	Sheehan syndrome (postpartum pituitary necrosis).
Uterine bleeding at 18 weeks' gestation; no products expelled; cervical os open.	Inevitable abortion.
Uterine bleeding at 18 weeks' gestation; no products expelled; cervical os closed.	Threatened abortion.

GYNECOLOGY

The first test to perform when a woman presents with amenorrhea.	β-hCG; the most common cause of amenorrhea is pregnancy.
Term for heavy bleeding during and between menstrual periods.	Menometrorrhagia.
Cause of amenorrhea with normal prolactin, no response to estrogen-progesterone challenge, and a history of D&C.	Asherman syndrome.
Therapy for polycystic ovarian syndrome.	Weight loss and OCPs. Consider metformin.
Medication used to induce ovulation.	Clomiphene citrate.
Diagnostic step required in a postmenopausal woman who presents with vaginal bleeding.	Endometrial biopsy.
Indications for medical treatment of ectopic pregnancy.	Patient stable; unruptured ectopic pregnancy of < 3.5 cm at < 6 weeks' gestation.
Medical options for endometriosis.	OCPs, danazol, GnRH agonists.
Laparoscopic findings in endometriosis.	Powder burns, "chocolate cysts."
The most common location for an ectopic pregnancy.	Ampulla of the oviduct.
How to diagnose and follow a leiomyoma.	Ultrasonography.
Natural history of a leiomyoma.	Regresses after menopause.
A patient has ↑ vaginal discharge and petechial patches in the upper vagina and cervix.	Trichomonal vaginitis.
Treatment for bacterial vaginosis.	Oral metronidazole.
The most common cause of bloody nipple discharge.	Intraductal papilloma.
Contraceptive methods that protect against PID.	OCPs and barrier contraception.
Unopposed estrogen is contraindicated in which cancers?	Endometrial or estrogen receptor–⊕ breast cancer.
A patient presents with recent PID with RUQ pain.	Consider Fitz-Hugh–Curtis syndrome.
Breast malignancy presenting as itching, burning, and erosion of the nipple.	Paget disease.

Annual screening for women with a strong family history of ovarian cancer.	CA-125 and transvaginal ultrasonography.
A 50-year-old woman leaks urine when laughing or coughing. Nonsurgical options?	Kegel exercises, estrogen, pessaries for stress incontinence.
A 30-year-old woman has unpredictable urine loss. Examination is normal. Medical options?	Anticholinergics (oxybutynin) or β-adrenergics (metaproterenol) for urge incontinence.
Lab values suggestive of menopause.	↑ serum FSH.
The most common cause of female infertility.	Endometriosis.
Two consecutive findings of typical squamous cells of undetermined significance (ASCUS) on Pap smear. Follow-up evaluation?	Colposcopy and endocervical curettage.
Breast cancer type that ↑ the future risk of invasive carcinoma in both breasts.	Lobular carcinoma in situ.

PEDIATRICS

Nontender abdominal mass associated with ↑ vanillylmandelic acid (VMA) and homovanillic acid (HVA).	Neuroblastoma.
The most common type of tracheoesophageal fistula (TEF). Classic presentation?	Esophageal atresia with distal TEF (85%). Unable to pass NG tube.
Not contraindications to vaccination.	Mild illness and/or low-grade fever, current antibiotic therapy, and prematurity.
Tests to rule out abusive head trauma.	Ophthalmologic exam, CT, and MRI.
A neonate has meconium ileus.	Cystic fibrosis (Hirschsprung disease is associated with failure to pass meconium for 48 hours).
Bilious emesis within hours after the first feeding.	Duodenal atresia.
A 2-month-old baby presents with nonbilious projectile emesis. Diagnosis? What are the appropriate steps in management?	Pyloric stenosis. Hydrate and correct metabolic abnormalities; then correct pyloric stenosis with pyloromyotomy.
The most common 1° immunodeficiency.	Selective IgA deficiency.
An infant has a high fever and onset of rash as fever breaks. What is he at risk for?	Febrile seizures (due to roseola infantum).
What is the immunodeficiency? ▪ A boy has chronic respiratory infections. Nitroblue tetrazolium test is ⊖. ▪ A child has eczema, thrombocytopenia, and high levels of IgA. ▪ A 4-month-old boy has life-threatening Pseudomonas infection.	 Chronic granulomatous disease. Wiskott-Aldrich syndrome. Bruton's X-linked agammaglobulinemia.

Acute-phase treatment for Kawasaki disease.	High-dose ASA for inflamm tion and fever; IVIG to prevent coronary artery aneurysms.
Treatment for mild and severe unconjugated hyperbilirubinemia.	Phototherapy (mild) or exchange transfusion (severe). (Do not use phototherapy for conjugated hyperbilirubinemia.)
Sudden onset of mental status changes, emesis, and liver dysfunction after ASA intake.	Reye syndrome.
A child has loss of red light refl x (white pupil). Diagnosis? The child has an ↑ risk of what cancer?	Suspect retinoblastoma. Osteosarcoma.
Vaccinations at a 6-month well-child visit.	HBV, DTaP, Hib, IPV, PCV, rotavirus.
Tanner stage 3 in a 6-year-old girl.	Precocious puberty.
Infection of small airways with epidemics in winter and spring.	RSV bronchiolitis.
Cause of neonatal RDS.	Surfactant deficien y.
Red "currant-jelly" stools, colicky abdominal pain, bilious vomiting, and a sausage-shaped mass in the RUQ.	Intussusception.
A congenital heart disease that causes 2° hypertension. What would you find on p ysical examination?	Coarctation of the aorta; ↓ femoral pulses.
First-line treatment for otitis media.	Amoxicillin.
The most common pathogen causing croup.	Parainfluenza virus ype 1.
A homeless child is small for his age and has peeling skin and a swollen belly.	Kwashiorkor (protein malnutrition).
Defect in an X-linked syndrome with mental retardation, gout, self-mutilation, and choreoathetosis.	Lesch-Nyhan syndrome (purine salvage problem with HGPRTase deficien y).
A newborn girl has a continuous "machinery murmur." What drug would you give?	Patent ductus arteriosus (PDA). Indomethacin is given to close the PDA.
A newborn girl with a posterior neck mass and swelling of the hands.	Turner syndrome.
A young child presents with proximal muscle weakness, waddling gait, and pronounced calf muscles.	Duchenne muscular dystrophy.
A firs -born female who was born in breech position is found to have asymmetric skin folds on newborn exam. Diagnosis? Treatment?	Developmental dysplasia of the hip. If severe, consider a Pavlik harness to maintain abduction.
An 11-year-old obese African American boy presents with sudden onset of limp. Diagnosis? Workup?	Slipped capital femoral epiphysis. AP and frog-leg lateral radiographs.
An active 13-year-old boy has anterior knee pain. Diagnosis?	Osgood-Schlatter disease.

PSYCHIATRY

First-line pharmacotherapy for depression.	SSRIs.
Antidepressants associated with hypertensive crisis.	MAOIs.
Galactorrhea, impotence, menstrual dysfunction, and ↓ libido.	Dopamine antagonists.
A 17-year-old girl has left arm paralysis after her boyfriend dies in a car crash. No medical cause is found.	Conversion disorder.
Name the defense mechanism: ▪ A mother who is angry at her husband yells at her child. ▪ A girl who is upset with her best friend acts overly kind. ▪ A man calmly describes a grisly murder. ▪ A hospitalized 10-year-old begins to wet his bed.	 Displacement. Reaction formation. Isolation. Regression.
Life-threatening muscle rigidity, high fever, autonomic instability, confusion, and elevated creatine phosphokinase.	Neuroleptic malignant syndrome.
Amenorrhea, low body weight (< 85%), bradycardia, and abnormal body image in a young woman.	Anorexia.
A 35-year-old man has recurrent episodes of palpitations, diaphoresis, and fear of impending doom..	Panic disorder.
The most serious side effect of clozapine.	Agranulocytosis.
A 21-year-old man has 3 months of social withdrawal, worsening grades, flattened affect, and concrete thinking.	Schizophreniform disorder (a diagnosis of schizophrenia requires ≥ 6 months of symptoms).
Key side effects of atypical antipsychotics.	Weight gain, type 2 DM, QT-segment prolongation.
A young weight lifter receives IV haloperidol and complains that his eyes are deviated sideways. Diagnosis? Treatment?	Acute dystonia (oculogyric crisis). Treat with benztropine or diphenhydramine.
Medication to avoid in patients with a history of alcohol withdrawal seizures.	Neuroleptics, which can lower the seizure threshold.
A 13-year-old boy has a history of theft, vandalism, and violence toward family pets.	Conduct disorder. Associated with antisocial personality disorder in adults.
A 5-month-old girl has ↓ head growth, truncal discoordination, and ↓ social interaction.	Rett disorder. Loss of milestones is commonly described.
A patient hasn't slept for days, lost $20,000 gambling, is agitated, and has pressured speech. Diagnosis? Treatment?	Acute mania. Start a mood stabilizer (eg, lithium).
After a minor "fender bender," a man wears a neck brace and requests permanent disability.	Malingering.

A nurse presents with severe hypoglycemia; blood analysis reveals no elevation in C-peptide.	Factitious disorder.
A patient spends most of his time acquiring cocaine despite losing his job and being threatened with legal charges.	Substance use disorder.
Medication to avoid in patients with PTSD.	Benzodiazepines (have high addiction potential). Patients commonly have a history of substance abuse.
A violent patient has vertical and horizontal nystagmus.	Phencyclidine hydrochloride (PCP) intoxication.
A woman who was abused as a child frequently feels outside of or detached from her body.	Depersonalization disorder.
A schizophrenic patient takes haloperidol for 1 year and develops uncontrollable tongue movements. Diagnosis? Treatment?	Tardive dyskinesia. ↓ or discontinue haloperidol and consider another antipsychotic (eg, risperidone, clozapine).
A man with major depressive disorder is counseled to avoid tyramine-rich foods with his new medication. What class of medications is he taking?	MAOIs.

PULMONARY

Risk factors for DVT.	Stasis, endothelial injury, and hypercoagulability (Virchow triad).
Criteria for exudative effusion	Pleural/serum protein > 0.5; pleural/serum LDH > 0.6.
Causes of exudative effusion	Think of leaky capillaries. Malignancy, TB, bacterial or viral infection, pulmonary embolism (PE) with infarct, and pancreatitis.
Causes of transudative effusion	Think of intact capillaries. CHF, liver or kidney disease, and protein-losing enteropathy.
Normalizing P_{CO_2} in a patient having an asthma exacerbation may indicate _____.	Fatigue and impending respiratory failure.
Treatment for acute asthma and COPD exacerbations.	β_2-agonists and corticosteroids (anticholinergics and antibiotics for COPD exacerbation as well).
Sarcoidosis.	Dyspnea, lateral hilar lymphadenopathy on chest radiograph, noncaseating granulomas, ↑ angiotensin-converting enzyme, and hypercalcemia.
PFTs of obstructive pulmonary disease.	↓ FEV_1/FVC.
PFTs of restrictive pulmonary disease.	↑ FEV_1/FVC, ↓ TLC.
Honeycomb pattern on chest radiograph. Treatment?	Diffuse interstitial pulmonary fibrosis. Supportive care; antifibrotic agents may help.
Treatment for SVC syndrome.	Radiation.
Treatment for mild persistent asthma.	Inhaled β-agonists and inhaled corticosteroids.

Treatment for COPD exacerbation.	O_2, bronchodilators, antibiotics, corticosteroids with taper, smoking cessation.
Treatment for chronic COPD.	Smoking cessation, home O_2, β-agonists, anticholinergics, systemic or inhaled corticosteroids, flu and pneumo occal vaccines.
Acid-base disorder in PE.	Respiratory alkalosis with hypoxia and hypocarbia.
Non–small cell lung cancer (NSCLC) associated with hypercalcemia.	Squamous cell carcinoma.
Lung cancer associated with syndrome of inappropriate antidiuretic hormone (SIADH).	Small cell lung cancer (SCLC).
Lung cancer associated with Lambert Eaton syndrome.	SCLC.
Lung cancers highly related to cigarette exposure.	SCLC, SCC.
A tall Caucasian man presents with acute shortness of breath. Diagnosis? Treatment?	Spontaneous pneumothorax. Spontaneous regression; supplemental O_2 may be helpful.
Treatment of tension pneumothorax.	Immediate needle thoracostomy (over diagnostic).
Characteristics favoring carcinoma in an isolated pulmonary nodule.	Age > 45–50; tobacco use; lesions new or larger in comparison to old films; absen e of calcific tion or irregular calcific tion; size > 2 cm; irregular margins.
ARDS.	Hypoxemia and pulmonary edema with normal pulmonary capillary wedge pressure (PCWP).
Sequelae of asbestos exposure.	Pulmonary fib osis, pleural plaques, bronchogenic carcinoma (mass in lung field), mesothelioma (pleu al mass).
↑ risk of what infection with silicosis?	Mycobacterium tuberculosis.
Causes of hypoxemia.	Right-to-left shunt, hypoventilation, low inspired O_2 tension, diffusion defect, V/Q mismatch.
Classic chest radiographic findings or pulmonary edema.	Cardiomegaly, prominent pulmonary vessels, Kerley B lines, "bat's-wing" appearance of hilar shadows, and perivascular and peribronchial cuffi .
Chest radiography findings suggesti e of PE.	Westermark sign and Hampton hump.

RENAL/GENITOURINARY

Renal tubular acidosis (RTA) associated with abnormal H^+ secretion and nephrolithiasis.	Type I (distal) RTA.
RTA associated with abnormal HCO_3^- reabsorption and rickets.	Type II (proximal) RTA.
RTA associated with low aldosterone state.	Type IV (distal) RTA.

Treatment of hypernatremia.	NS if unstable vital signs; D5W or ½ NS to replace free-water loss.
Differential diagnosis of hypotonic hypervolemic hyponatremia.	Cirrhosis, CHF, nephrotic syndrome, acute kidney injury (AKI), chronic kidney disease (CKD).
Chvostek and Trousseau signs.	Hypocalcemia.
The most common causes of hypercalcemia.	Malignancy and hyperparathyroidism.
T-wave flattening and U waves.	Hypokalemia.
Peaked T waves and widened QRS.	Hyperkalemia.
Treatment of hyperkalemia.	C BIG K (calcium gluconate, bicarb, insulin, glucose, kayexalate).
First-line treatment for moderate hypercalcemia.	IV hydration.
Type of AKI in a patient with $Fe_{Na} < 1\%$.	Prerenal.
A 49-year-old man presents with acute-onset flank pain and hematuria.	Nephrolithiasis.
The most common type of nephrolithiasis.	Calcium oxalate.
Test of choice for nephrolithiasis.	Noncontrast CT.
Ultrasonography shows bilateral enlarged kidneys with cysts. Associated brain anomaly?	Cerebral berry aneurysms (autosomal dominant polycystic kidney disease, PCKD).
Hematuria, hypertension, and oliguria.	Nephritic syndrome.
Proteinuria, hypoalbuminemia, hyperlipidemia, hyperlipiduria, and edema.	Nephrotic syndrome.
The most common form of nephrotic syndrome in adults.	Focal segmental glomerulosclerosis.
Nephritic syndrome presenting 3 days after URI, **normal C3.**	IgA nephropathy (Berger disease).
Palpable purpura, arthralgias, abdominal pain.	Henoch-Schönlein purpura.
Glomerulonephritis with deafness.	Alport syndrome.
Glomerulonephritis with hemoptysis.	Granulomatosis with polyangiitis and Goodpasture syndrome.
Presence of red cell casts in urine sediment.	Glomerulonephritis/nephritic syndrome.
Eosinophils in urine sediment.	Allergic interstitial nephritis.
Waxy casts in urine sediment and Maltese crosses (seen with lipiduria).	Nephrotic syndrome.
Muddy brown casts.	Acute tubular necrosis.
Drowsiness, asterixis, nausea, and a pericardial friction rub.	Uremic syndrome seen in patients with renal failure.

A 55-year-old man is diagnosed with prostate cancer. Treatment options?	Wait, surgical resection, radiation therapy, and/or androgen suppression.
Hematuria in a 50-year-old smoker.	Bladder cancer.
Hematuria, flank pain, and palpable flank ma .	Renal cell carcinoma (RCC).
Testicular cancer associated with β-hCG.	Choriocarcinoma.
The most common type of testicular cancer.	Seminoma, a type of germ cell tumor.
The most common histology of bladder cancer.	Transitional cell carcinoma.
Complication of overly rapid correction of hyponatremia.	Central pontine myelinolysis.
Salicylate ingestion occurs in what type of acid-base disorder?	Anion gap acidosis and 1° respiratory alkalosis due to central respiratory stimulation.
Acid-base disturbance commonly seen in pregnant women.	Respiratory alkalosis.
A 55-year-old man presents with irritative and obstructive urinary symptoms. Treatment options?	Probably BPH. Options include no treatment, terazosin, finas eride, or surgical intervention (TURP).

SELECTED TOPICS IN EMERGENCY MEDICINE

Class of drugs that may cause syndrome of muscle rigidity, hyperthermia, autonomic instability, and extrapyramidal symptoms.	Antipsychotics (neuroleptic malignant syndrome).
Side ef ects of corticosteroids.	Acute mania, immunosuppression, thin skin, osteoporosis, easy bruising, myopathies.
Treatment for DTs.	Benzodiazepines.
Treatment for acetaminophen overdose.	N-acetylcysteine.
Treatment for opioid overdose.	Naloxone.
Treatment for benzodiazepine overdose.	Flumazenil (monitor for withdrawal and seizures).
Treatment for neuroleptic malignant syndrome and malignant hyperthermia.	Dantrolene.
Treatment for malignant hypertension.	Nitroprusside.
Treatment of atrial fib illation.	Rate control, rhythm conversion, and anticoagulation.
Treatment of supraventricular tachycardia.	If stable, rate control with carotid massage or other vagal stimulation; if unsuccessful, consider adenosine.
Causes of drug-induced SLE.	INH, penicillamine, hydralazine, procainamide, chlorpromazine, methyldopa, quinidine.

Macrocytic, megaloblastic anemia with neurologic symptoms.	B_{12} deficien y.
Macrocytic, megaloblastic anemia without neurologic symptoms.	Folate deficien y.
A burn patient presents with cherry-red, flushed s in and coma. Sa_{o_2} is normal, but carboxyhemoglobin is elevated. Treatment?	Treat CO poisoning with 100% O_2 or with hyperbaric O_2 if poisoning is severe or the patient is pregnant.
Blood in the urethral meatus or high-riding prostate.	Bladder rupture or urethral injury.
Test to rule out urethral injury.	Retrograde cystourethrogram.
Radiographic evidence of aortic disruption or dissection.	Widened mediastinum (> 8 cm), loss of aortic knob, pleural cap, tracheal deviation to the right, depression of left main stem bronchus.
Radiographic indications for surgery in patients with acute abdomen.	Free air under the diaphragm, extravasation of contrast, severe bowel distention, space-occupying lesion (CT), mesenteric occlusion (angiography).
The most common organism in burn-related infections.	Pseudomonas.
Method of calculating fluid epletion in burn patients.	Parkland formula: 24-hour fluids = 4 × kg × % BSA.
Acceptable urine output in a trauma patient.	50 cc/hr.
Acceptable urine output in a stable patient.	30 cc/hr.
Signs of neurogenic shock.	Hypotension and bradycardia.
Signs of ↑ ICP (Cushing triad).	Hypertension, bradycardia, and abnormal respirations.
↓ CO, ↓ PCWP, ↑ peripheral vascular resistance (PVR).	Hypovolemic shock.
↓ CO, ↑ PCWP, ↑ PVR.	Cardiogenic (or obstructive) shock.
↑ CO, ↓ PCWP, ↓ PVR.	Distributive (eg, septic or anaphylactic) shock.
Treatment of septic shock.	Fluids and antibiotics.
Treatment of cardiogenic shock.	Identify cause; inotropes (eg, dopamine).
Treatment of hypovolemic shock.	Identify cause; fluid and blood epletion.
Treatment of anaphylactic shock.	Epinephrine 1:1000 and diphenhydramine.
Supportive treatment for ARDS.	Low tidal volume ventilation.
Signs of air embolism.	A patient with chest trauma who was previously stable suddenly dies.
Signs of cardiac tamponade.	Distended neck veins, hypotension, diminished heart sounds (Beck triad); pulsus paradoxus.
Absent breath sounds, dullness to percussion, shock, fl t neck veins.	Massive hemothorax.

Absent breath sounds, tracheal deviation, shock, distended neck veins.	Tension pneumothorax.
Treatment for blunt or penetrating abdominal trauma in hemodynamically unstable patients.	Immediate exploratory laparotomy.
↑ ICP in alcoholics or the elderly following head trauma. Can be acute or chronic; crescent shape on CT.	Subdural hematoma.
Head trauma with immediate loss of consciousness followed by a lucid interval and then rapid deterioration. Convex shape on CT.	Epidural hematoma.

SECTION 3

TOP-RATED REVIEW RESOURCES

How to Use the Database 544

Disclaimer/Conflict-of-Interest Statement 545

Comprehensive 546

Question Banks 546

Internal Medicine, Emergency Medicine, Family Medicine 547

Neurology 547

OB/GYN 548

Pediatrics 548

Psychiatry 548

Surgery 549

Commercial Review Courses 550

How to Use the Database

This section is a database of recommended clinical science review resources, question banks, and other test preparation tools marketed to medical students studying for the USMLE Step 2 CK. For each resource, we list the **Title**, the **First Author** (or editor), the **Current Publisher,** the **Copyright Year,** the **Edition,** the **Number of Pages,** the **ISBN,** the **Approximate List Price,** the **Format** of the resource, and the **Number of Test Questions.** Finally, each resource receives a **Rating.** The resources are sorted into a comprehensive section as well as into sections corresponding to the six clinical disciplines (internal medicine, neurology, OB/GYN, pediatrics, psychiatry, and surgery). Within each section, resources are arranged first by Rating, then by Author, and finally by Title.

For this ninth edition of First Aid for the USMLE Step 2 CK, the database of review resources has been completely revised, with in-depth summary comments on more than 100 books and online and mobile applications. A letter rating scale with six different grades reflects the detailed student evaluations. Each resource receives a rating as follows:

A+	Excellent for boards review.
A A–	Very good for boards review; choose among the group.
B+ B	Good, but use only after exhausting better sources.
B–	Fair, but there are many better books in the discipline; or low-yield subject material.

The **Rating** is meant to reflect the overall usefulness of the resource in preparing for the USMLE Step 2 CK exam. This is based on a number of factors, including:

- The cost of the resource
- The readability of the text
- The appropriateness and accuracy of the resource
- The quality and number of sample questions
- The quality of written answers to sample questions
- The quality and appropriateness of the illustrations (eg, graphs, diagrams, photographs)
- The length of the text (longer is not necessarily better)
- The quality and number of other resources available in the same discipline
- The importance of the discipline on the USMLE Step 2 CK exam

Please note that **the rating does not reflect the quality of the resource for purposes other than reviewing for the USMLE Step 2 CK exam.** Many resources with low ratings are well written and informative but are not ideal for USMLE Step 2 CK preparation. We have also avoided listing or commenting on the wide variety of general textbooks available in the clinical sciences.

Evaluations are based on the cumulative results of formal and informal surveys of hundreds of medical students from medical schools across the country. The summary comments and overall ratings represent a consensus opinion, but there may have been a large range of opinions or limited student feedback on any particular resource. Please note that the data listed are subject to change.

We actively encourage medical students and faculty to submit their opinions and ratings of these clinical science review books so that we can update our database (see "How to Contribute," p. xiii). In addition, we ask that publishers and authors submit review copies of clinical science review books, including new editions, and books not included in our database, for evaluation. We also solicit reviews of new books or suggestions for alternate modes of study that may be useful in preparing for the examination, such as flash cards, computer-based tutorials, commercial review courses, and Internet Web sites.

DISCLAIMER/CONFLICT-OF-INTEREST STATEMENT

No material in this book, including the ratings, reflects the opinion or influence of the publisher. All errors and omissions will gladly be corrected if brought to the attention of the authors through our blog at www.firstaidteam.com. Please note that USMLE-Rx and the entire First Aid for the USMLE series are publications by the senior authors of this book; their ratings are based solely on recommendations from the student authors of this book as well as data from the student survey and feedback forms.

COMPREHENSIVE

		AUTHOR	PUBLISHER	TYPE	PRICE
A	Master the Boards USMLE Step 2 CK	Fischer	Kaplan Publishing, 2013, 2nd ed., 608 pages, ISBN 9781560536109	Review	$44.99
A	USMLE Step 2 Secrets	O'Connell	Elsevier, 2014, 4th ed., 368 pages, ISBN 9780323188142	Review	$48.95
A⁻	First Aid Cases for the USMLE Step 2 CK	Le	McGraw-Hill Education, 2010, 2nd ed., 543 pages, ISBN 9780071625708	Review	$45.00
A⁻	First Aid Q&A for the USMLE Step 2 CK	Le	McGraw-Hill Education, 2010, 2nd ed., 741 pages, ISBN 9780071625715	Review/Test/1000 q	$52.00
A⁻	Step-Up to USMLE Step 2	Van Kleunen	Lippincott Williams & Wilkins, 2014, 3rd ed., 352 pages, ISBN 9781451189599	Review	$53.99
B⁺	Boards & Wards for USMLE Steps 2 & 3	Ayala	Lippincott Williams & Wilkins, 2012, 5th ed., 608 pages, ISBN 9781451144062	Review	$53.99
B⁺	USMLE Step 2 Made Ridiculously Simple	Carl	Medmaster Books, 2012, 5th ed., 402 pages, ISBN 9780940780996	Review	$29.95
B⁺	Kaplan Medical USMLE Diagnostic Flashcards	Fischer	Kaplan Publishing, 2012, 3rd ed., 408 cards, ISBN 9781609780371	Flashcards	$44.99
B⁺	NMS Q&A Review for USMLE Step 2 CK	Ibsen	Lippincott Williams & Wilkins, 2012, 4th ed., 384 pages, ISBN 9780781787390	Review/Test/1000 q	$51.99
B⁺	Clinical Vignettes for the USMLE Step 2 CK: PreTest Self-Assessment & Review	McGraw-Hill	McGraw-Hill Education, 2009, 5th ed., 292 pages, ISBN 9780071604635	Test/368 q	$39.00
B	Physical Diagnosis: PreTest Self-Assessment & Review	Bernstein	McGraw-Hill Education, 2011, 7th ed., 442 pages, ISBN 9780071633017	Test/500 q	$37.00
B	USMLE Step 2 CK QBook	Kaplan Medical	Kaplan Publishing, 2014, 6th ed., 540 pages, ISBN 9781419550485	Test/850 q	$44.99
B	USMLE Steps 2 and 3: In Your Pocket	McWilliams	Kaplan Publishing, 2014, 2nd ed., 480 pages, ISBN 9781609788988	Review	$34.99
B	Déjà Review: USMLE Step 2 CK	Naheedy	McGraw-Hill Education, 2010, 2nd ed., 348 pages, ISBN 9780071627160	Review	$24.00
B	Brochert's Crush Step 2	O'Connell	Elsevier, 2013, 4th ed., 352 pages, ISBN 9781455703111	Review	$41.95
B	USMLE Step 2 Recall	Ryan	Lippincott Williams & Wilkins, 2010, 2nd ed., 385 pages, ISBN 9781605479071	Review	$45.99

QUESTION BANKS

		AUTHOR	PUBLISHER	PRICE
A⁺	UWorld Step 2 CK Qbank	Uworld	www.uworld.com	$149–$399
A	USMLE-Rx Step 2 Qmax	MedIQ Learning	www.usmle-rx.com	$98–$248
A⁻	Kaplan QBank	Kaplan	www.kaplanmedical.com	$99–$299
A⁻	USMLE Consult's Step 2 CK Question Bank	Elsevier	www.usmleconsult.com	$75–$175
B	USMLEasy	McGraw-Hill Education	www.usmle-easy.com	$39–$169

INTERNAL MEDICINE, EMERGENCY MEDICINE, FAMILY MEDICINE

		AUTHOR	PUBLISHER	TYPE	PRICE
A	Case Files: Emergency Medicine	Toy	McGraw-Hill Education, 2013, 3rd ed., 616 pages, ISBN 9780071768542	Review	$34.00
A–	Step-Up to Medicine	Agabegi	Lippincott Williams & Wilkins, 2013, 3rd ed., 576 pages, ISBN 9781609133603	Review	$57.99
A–	First Aid for the Medicine Clerkship	Kaufman	McGraw-Hill Education, 2010, 3rd ed., 420 pages, ISBN 9780071633826	Review	$49.00
A–	Emergency Medicine: PreTest Self-Assessment & Review	Rosh	McGraw-Hill Education, 2012, 3rd ed., 624 pages, ISBN 9780071773102	Test/500 q	$37.00
A–	First Aid for the Emergency Medicine Clerkship	Stead	McGraw-Hill Education, 2011, 3rd ed., 537 pages, ISBN 9780071739061	Review	$50.00
A–	Case Files: Family Medicine	Toy	McGraw-Hill Education, 2012, 3rd ed., 625 pages, ISBN 9780071753951	Review	$35.00
A–	Case Files: Internal Medicine	Toy	McGraw-Hill Education, 2013, 4th ed., 560 pages, ISBN 9780071761727	Review	$34.00
B+	Medical Secrets	Harward	Elsevier, 2012, 5th ed., 624 pages, ISBN 9780323063982	Review	$42.95
B+	Family Medicine: PreTest Self-Assessment & Review	Knutson	McGraw-Hill Education, 2012, 3rd ed., 303 pages, ISBN 9780071760522	Test/500 q	$33.00
B	Medicine Recall	Bergin	Lippincott Williams & Wilkins, 2011, 4th ed., 848 pages, ISBN 9781605476759	Review	$49.99
B	In A Page Emergency Medicine	Caterino	Lippincott Williams & Wilkins, 2003, 1st ed., 316 pages, ISBN 9781405103572	Review	$50.99
B	Déjà Review: Family Medicine	Perez	McGraw-Hill Education, 2011, 2nd ed., 402 pages, ISBN 9780071715157	Review	$24.00
B	Déjà Review: Internal Medicine	Saadat	McGraw-Hill Education, 2011, 2nd ed., 254 pages, ISBN 9780071715171	Review	$24.00
B	Medicine: PreTest Self-Assessment & Review	Smalligan	McGraw-Hill Education, 2012, 13th ed., 470 pages, ISBN 9780071761499	Test/500 q	$37.00
B	Blueprints Medicine	Young	Lippincott Williams & Wilkins, 2009, 5th ed., 448 pages, ISBN 9780781788700	Review/Test/100 q	$48.99
B–	Déjà Review: Emergency Medicine	Jang	McGraw-Hill Education, 2011, 2nd ed., 480 pages, ISBN 9780071715188	Review	$24.00

NEUROLOGY

		AUTHOR	PUBLISHER	TYPE	PRICE
A–	Blueprints Neurology	Drislane	Lippincott Williams & Wilkins, 2013, 4th ed., 256 pages, ISBN 9781451117684	Review/Test/100 q	$51.99
B+	Neurology: PreTest Self-Assessment & Review	Anschel	McGraw-Hill Education, 2012, 8th ed., 358 pages, ISBN 9780071761147	Test/500 q	$37.00
B	Neurology Secrets	Rolak	Elsevier, 2010, 5th ed., 486 pages, ISBN 9780323057127	Review	$59.95
B	Blueprints Clinical Cases in Neurology	Sheth	Lippincott Williams & Wilkins, 2007, 2nd ed., 390 pages, ISBN 9781405104944	Test/200 q	$43.99

OB/GYN

		AUTHOR	PUBLISHER	TYPE	PRICE
A⁻	Blueprints Obstetrics and Gynecology	Callahan	Lippincott Williams &Wilkins, 2013, 6th ed., 432 pages, ISBN 9781451117028	Review/Test/150 q	$48.99
A⁻	Case Files: Obstetrics and Gynecology	Toy	McGraw-Hill Education, 2013, 4th ed., 540 pages, ISBN 9780071761710	Review	$36.00
B⁺	First Aid for the Obstetrics &Gynecology Clerkship	Kaufman	McGraw-Hill Education, 2011, 3rd ed., 493 pages, ISBN 9780071634199	Review	$50.00
B⁺	Obstetrics and Gynecology: PreTest Self-Assessment & Review	Schneider	McGraw-Hill Education, 2012, 13th ed., 352 pages, ISBN 9780071761277	Test/500 q	$37.00
B	Déjà Review: Obstetrics and Gynecology	Miller	McGraw-Hill Education, 2011, 2nd ed., 490 pages, ISBN 9780071715133	Review	$24.00
B	NMS Obstetrics and Gynecology	Pfeifer	Lippincott Williams &Wilkins, 2011, 7th ed., 528 pages, ISBN 9781608315765	Review/Test/500 q	$56.99
B⁻	Lange Q&A: Obstetrics and Gynecology	Katz	McGraw-Hill Education, 2011, 9th ed., 404 pages, ISBN 9780071712132	Test/1300+ q	$53.00

PEDIATRICS

		AUTHOR	PUBLISHER	TYPE	PRICE
A⁻	First Aid for the Pediatrics Clerkship	Stead	McGraw-Hill Education, 2011, 3rd ed., 607 pages, ISBN 9780071664035	Review	$45.00
A⁻	Case Files: Pediatrics	Toy	McGraw-Hill Education, 2013, 4th ed., 479 pages, ISBN 9780071766982	Review	$34.00
A⁻	Pediatrics: PreTest Self-Assessment &Review	Yetman	McGraw-Hill Education, 2013, 13th ed., 422 pages, ISBN 9780071761239	Test/500 q	$37.00
B⁺	Déjà Review: Pediatrics	Davey	McGraw-Hill Education, 2011, 2nd ed., 307 pages, ISBN 9780071715140	Review	$24.00
B	Blueprints Pediatrics	Marino	Lippincott Williams &Wilkins, 2013, 6th ed., 416 pages, ISBN 9781451116045	Review/Test/100 q	$48.99
B	Pediatric Secrets	Polin	Elsevier, 2011, 5th ed., 640 pages, ISBN 9780323065610	Review	$39.95
B⁻	Lange Q&A: Pediatrics	Jackson	McGraw-Hill Education, 2010, 7th ed., 326 pages, ISBN 9780071475686	Test/1000 q	$55.00
B⁻	Pediatrics Recall	McGahren	Lippincott Williams &Wilkins, 2011, 4th ed., 542 pages, ISBN 9781605476766	Review	$46.99

PSYCHIATRY

		AUTHOR	PUBLISHER	TYPE	PRICE
A	First Aid for the Psychiatry Clerkship	Stead	McGraw-Hill Education, 2011, 3rd ed., 230 pages, ISBN 9780071739238	Review	$50.00
A⁻	Psychiatry: PreTest Self-Assessment &Review	Klamen	McGraw-Hill Education, 2012, 13th ed., 291 pages, ISBN 9780071761017	Test/500 q	$37.00
A⁻	Case Files: Psychiatry	Toy	McGraw-Hill Education, 2012, 4th ed., 522 pages, ISBN 9780071766999	Review	$35.00

B+	Blueprints Psychiatry	Murphy	Lippincott Williams &Wilkins, 2009, 5th ed., 176 pages, ISBN 9780781782531	Review/Test/100 q	$50.99
B+	Lange Q&A: Psychiatry	Oransky	McGraw-Hill Education, 2011, 10th ed., 277 pages, ISBN 9780071703451	Test/800+ q	$53.00
B	NMS Psychiatry	Thornhill	Lippincott Williams &Wilkins, 2011, 6th ed., 303 pages, ISBN 9781608315741	Review/Test/500 q	$56.99
B–	Déjà Review: Psychiatry	Gopal	McGraw-Hill Education, 2011, 2nd ed., 244 pages, ISBN 9780071715164	Review	$24.00

SURGERY

		AUTHOR	PUBLISHER	TYPE	PRICE
A	Dr. Pestana's Surgical Notes: Top 180 Vignettes for the Surgical Wards	Pestana	Kaplan Publishing, 2013, 1st ed., 240 pages, ISBN 9781609789169	Review	$39.95
A–	Case Files: Surgery	Toy	McGraw-Hill Education, 2012, 4th ed., 522 pages, ISBN 0071766995	Review	$35.00
B+	First Aid for the Surgery Clerkship	Kaufman	McGraw-Hill Education, 2009, 2nd ed., 537 pages, ISBN 9780071448710	Review	$51.00
B+	Step-Up to Surgery	Zaslau	Lippincott Williams &Wilkins, 2014, 2nd ed., 408 pages, ISBN 9781451187632	Review	$54.99
B	Surgical Recall	Blackbourne	Lippincott Williams &Wilkins, 2014, 7th ed., 824 pages, ISBN 9781451192919	Review	$56.99
B	NMS Surgery	Jarrell	Lippincott Williams &Wilkins, 2008, 5th ed., 647 pages, ISBN 9780781759014	Review/Test/350 q	$51.99
B	Surgery: PreTest Self-Assessment &Review	Kao	McGraw-Hill Education, 2012, 13th ed., 374 pages, ISBN 9780071761215	Test/500 q	$37.00
B	Déjà Review: Surgery	Tevar	McGraw-Hill Education, 2012, 2nd ed., 412 pages, ISBN 0071715126	Review	$24.00
B–	Abernathy's Surgical Secrets	Harken	Elsevier, 2009, 6th ed., 517 pages, ISBN 9780323057110	Review	$44.95
B–	Blueprints in Surgery	Karp	Lippincott Williams &Wilkins, 2008, 5th ed., 253 pages, ISBN 9780781788687	Review/Test/100 q	$50.99

COMMERCIAL REVIEW COURSES

Although commercial preparation courses can be helpful for some students, such courses are typically costly and require significant time commitment. They are usually most effective as an organizing tool for students who feel overwhelmed by the sheer volume of material involved in Step 2 CK preparation. Note, too, that multiweek courses may be quite intense and may thus leave limited time for independent study. Also note that some commercial courses are designed for first-time test takers while others focus on students who are repeating the exam. In addition, some courses are geared toward IMGs who want to take all three Steps in a limited amount of time.

Student experience and satisfaction with review courses are highly variable. We suggest that you discuss options with recent graduates of the review courses you are considering. In addition, course content and structure can change rapidly. Some student opinions can be found in discussion groups on the World Wide Web. Listed below is contact information for some Step 2 CK commercial review courses.

Becker Professional Education
3005 Highland Parkway
Downers Grove, IL 60515
Phone: (800) 683-8725
http://www.becker.com

Kaplan Medical
6301 Kaplan University Ave.
Fort Lauderdale, FL 33309
Phone: (800) KAP-TEST (800-527-8378)
Email: customer.care@kaplan.com
http://www.kaptest.com

Med School Tutors
641 Lexington Ave.
New York, NY 10022
Phone: (212) 327-0098
Fax: (347) 658-5978
Email: scorehigh@medschooltutors.com
http://www.medschooltutors.com

Northwestern Medical Review
4800 Collins Rd. #22174
Lansing, MI 48909
Phone: (517) 347-6914
Fax: (517) 347-7005
Email: contactus@northwesternmedicalreview.com
http://www.northwesternmedicalreview.com

PASS Program
2302 Moreland Blvd.
Champaign, IL 61822
Phone: (217) 378-8018
Fax: (217) 378-7809
http://www.pass-program.com

Youel's Prep, Inc.
P.O. Box 31479
Palm Beach Gardens, FL 33420
Phone: (800) 645-3985
Fax: (561) 622-4858
Email: info@youelsprep.com
http://www.youelsprep.net

NOTES

About the Authors

Tao Le, MD, MHS



Tao developed a passion for medical education as a medical student. He currently edits more than 15 titles in the First Aid series. In addition, he is the founder and editor of the USMLE-Rx test bank and online video series as well as a cofounder of the Underground Clinical Vignettes series. As a medical student, he was editor-in-chief of the University of California, San Francisco (UCSF) Synapse, a university newspaper with a weekly circulation of 9000. Tao earned his medical degree from UCSF in 1996 and completed his residency training in internal medicine at Yale University and fellowship training at Johns Hopkins University. Tao subsequently went on to cofound Medsn, a medical education technology venture, and served as its chief medical officer. He is currently conducting research in asthma education at the University of Louisville.

Vikas Bhushan, MD



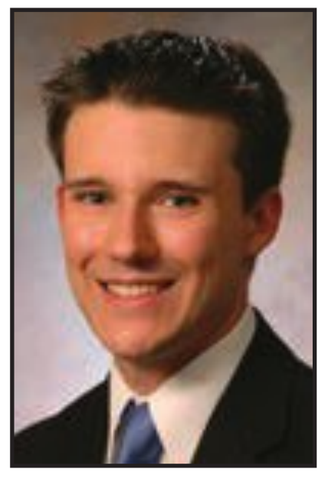
Vikas is a writer, editor, entrepreneur, and teleradiologist on sabbatical. In 1990 he conceived and authored the original First Aid for the USMLE Step 1. His entrepreneurial endeavors include a student-focused medical publisher (S2S), an e-learning company (medschool.com/Medsn), and an ER teleradiology practice (24/7 Radiology). Firmly anchored to the Left Coast, Vikas completed a bachelor's degree at the University of California, Berkeley; an MD with thesis at UCSF; and a diagnostic radiology residency at UCLA. His eclectic interests include technology, information design, photography, South Asian diasporic culture, and avoiding a day job. Always finding the long shortcut, Vikas is an adventurer, knowledge seeker, and occasional innovator. He enjoys novice status as a kiteboarder and single father, and strives to raise his children as global citizens.

Vincent L. Chen, MD



Vincent is currently a resident in internal medicine at Stanford University Medical Center. Outside the hospital, he enjoys photography, reading and watching Shakespearean plays, and exploring the Bay Area's many attractions. Vincent completed his bachelor's degree in chemistry at Amherst College and his medical degree at Harvard Medical School, where he graduated magna cum laude. Between college and medical school, he spent a year as a Fulbright fellow in Frankfurt, Germany. He has worked on multiple basic science research projects, most recently in intestinal immunology, as well as clinical research in liver cancer. He plans to specialize in gastroenterology.

Michael R. King, MD



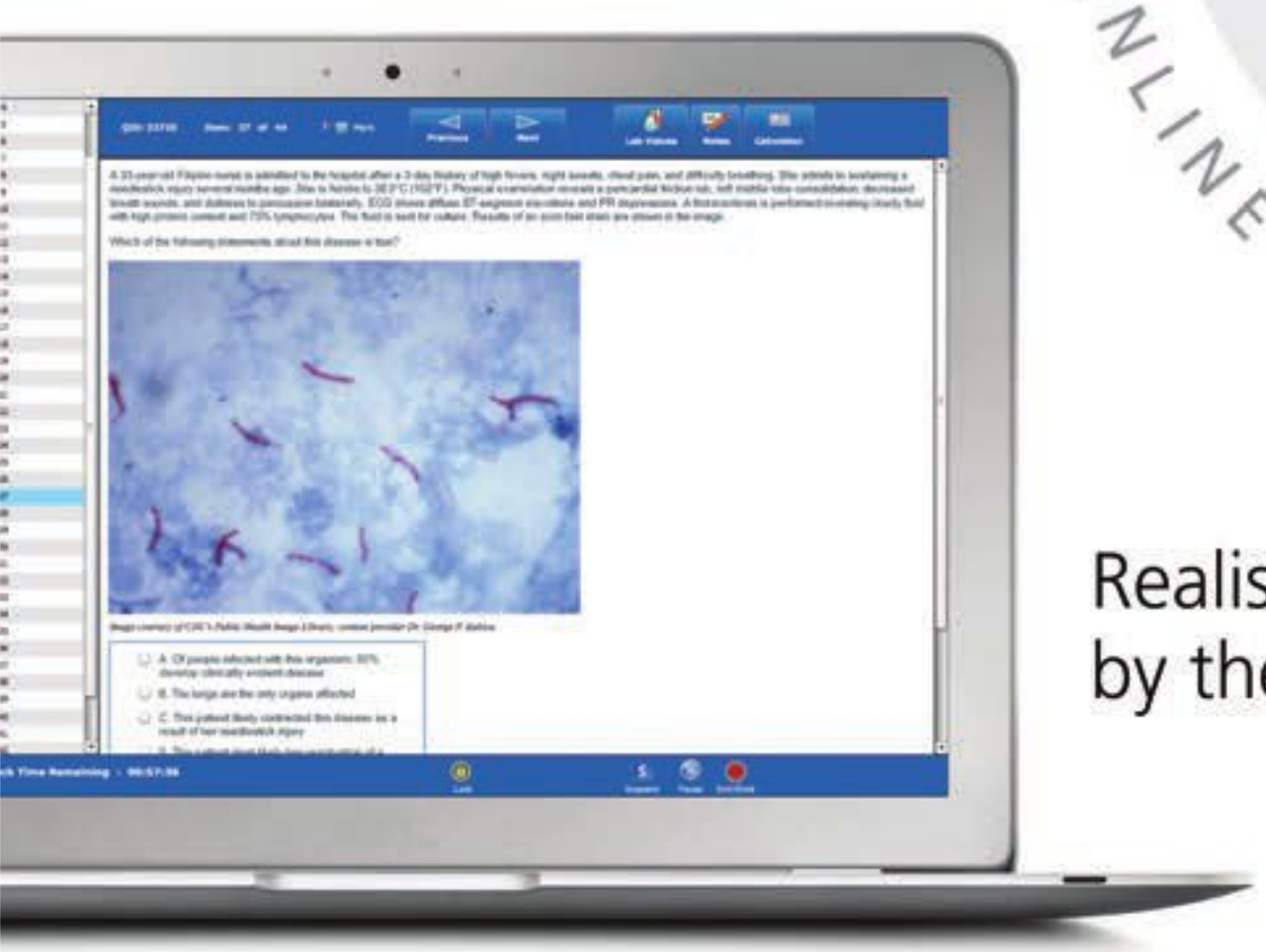
Originally from Naperville, Illinois, Michael studied molecular biology at the University of Illinois at Urbana-Champaign, attended medical school at the University of Chicago's Pritzker School of Medicine, and completed his internship in medicine at Albert Einstein Medical Center in Philadelphia. Michael is currently a resident in anesthesiology at the Massachusetts General Hospital and a clinical fellow at Harvard Medical School, both in Boston. He plans a career in pediatric anesthesiology and will be a fellow at the Children's Hospital of Philadelphia starting in late 2015. Michael began working on the First Aid series in 2009 and has contributed to projects on each of the USMLE exams. His hobbies outside of work include reading nonfiction, working out, and traveling.

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